THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellants:	Pridmore-Merten
Appl. No.:	10/597,436
Conf. No.:	1948
Filed:	August 22, 2008
Title:	NUTRITIONAL COMPOSITION FOR IMPROVING SKIN CONDITION AND PREVENTING SKIN DISEASES
Art Unit:	1657
Examiner:	Lisa J. Hobbs
Docket No.:	3712036-00745

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' APPEAL BRIEF

Sir:

Appellants submit this Appeal Brief in support of the Notice of Appeal filed on September 10, 2010. This Appeal is taken from the final Rejection dated June 29, 2010.

I. REAL PARTY IN INTEREST

The real party in interest for the above-identified patent application on Appeal is Nestec S.A. by virtue of an Assignment dated August 22, 2008 and recorded at reel 021427, frame 0119 in the United States Patent and Trademark Office.

II. RELATED APPEALS AND INTERFERENCES

Appellants' legal representative and the Assignee of the above-identified patent application do not know of any prior or pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision with respect to the above-identified Appeal.

III. STATUS OF CLAIMS

Claims 1-8, 12-16, 18-21, 31-33, 35-37 and 39-40 are pending in the above-identified patent application. Claims 9-11, 17, 22-30, 34 and 38 were previously canceled without prejudice or disclaimer. Claims 1-8, 12-16, 18-21, 31-33, 35-37 and 39-40 stand rejected. Therefore, Claims 1-8, 12-16, 18-21, 31-33, 35-37 and 39-40 are being appealed in this Brief. A copy of the appealed claims is included in the Claims Appendix.

IV. STATUS OF AMENDMENTS

A non-final Office Action was mailed on December 30, 2009, in which the Examiner rejected Claims 1-8, 12-21, 31-33, 35-37 and 39-40 under 35 U.S.C. §103. Appellants filed a Response to the non-final Office Action on March 30, 2010, in which Appellants argued against the obviousness rejections. A final Office Action was mailed on June 29, 2010, in which the Examiner maintained the rejections of Claims 1-8, 12-16, 18-21, 31-33, 35-37 and 39-40 under 35 U.S.C. §103. Appellants filed a Notice of Appeal on September 10, 2010. Copies of the non-final Office Action and final Office Action are included in the Evidence Appendix as Exhibits A and B, respectively.

V. SUMMARY OF CLAIMED SUBJECT MATTER

A summary of the invention by way of reference to the specification (WO 2005/074719) and/or figures for each of the independent claims is provided as follows:

Claim 1 is directed to a method for the stimulation of the lipid metabolism in the skin of an animal or a human being for treating dermatitis (page 1, lines 4-10; page 3, lines 2-8) comprising administering an ingestible composition comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine (page 1, lines 4-10; page 3, line 29-page 4, line 11; page 5, line 1-page 6, line 2; Example 1), wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight (page 4, lines 13-21) and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight (page 4, lines 28-30).

Claim 4 is directed to a method for the stimulation of the lipid metabolism in the skin of an animal or a human for preventing the onset or incidence of ulcers associated with diabetes, of circulation disturbances, of physical, chemical or microbial noxae or of eczema (page 1, lines 4-10; page 3, lines 2-8), comprising the steps of administering to a patient at risk of ulcers an ingestible composition comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine (page 1, lines 4-10; page 3, line 29-page 4, line 11; page 5, line 1-page 6, line 2; Example 1), wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight (page 4, lines 13-21) and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight (page 4, lines 28-30).

Claim 5 is directed to a method for the stimulation of the lipid metabolism in the skin of an animal or a human being for a reduction of itching (page 1, lines 4-10; page 3, lines 2-8) comprising the steps of administering to a patient that is itching due to a skin condition an ingestible composition comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine (page 1, lines 4-10; page 3, line 29-page 4, line 11; page 5, line 1-page 6, line 2; Example 1), wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight (page 4, lines 13-21) and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight (page 4, lines 28-30).

Claim 6 is directed to a method for making an ingestible composition for the stimulation of the lipid metabolism in the skin of an animal or a human being (page 1, lines 4-10; page 3,

lines 2-8), comprising the step of using L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine to make the composition (page 1, lines 4-10; page 3, line 29-page 4, line 11; page 5, line 1-page 6, line 2; Example 1), wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight (page 4, lines 13-21) and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight (page 4, lines 28-30).

Claim 18 is directed to an ingestible composition selected from the group consisting of a medicament, a food, a functional food, a nutritional complete pet or human food, and a dietary supplement (page 1, lines 4-10; page 3, lines 2-8) comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine (page 1, lines 4-10; page 3, line 29-page 4, line 11; page 5, line 1-page 6, line 2; Example 1), wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight (page 4, lines 13-21) and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight (page 4, lines 28-30).

Although specification citations are given in accordance with C.F.R. 1.192(c), these reference numerals and citations are merely examples of where support may be found in the specification for the terms used in this section of the Brief. There is no intention to suggest in any way that the terms of the claims are limited to the examples in the specification. As demonstrated by the references numerals and citations below, the claims are fully supported by the specification as required by law. However, it is improper under the law to read limitations from the specification into the claims. Pointing out specification support for the claim terminology as is done here to comply with rule 1.192(c) does not in any way limit the scope of the claims to those examples from which they find support. Nor does this exercise provide a mechanism for circumventing the law precluding reading limitations into the claims from the specification. In short, the references numerals and specification citations are not to be construed as claim limitations or in any way used to limit the scope of the claims.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Claims 1-8, 12-16, 18-21, 31-33, 35-37 and 39-40 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,380,252 to De Simone ("*De Simone*"), U.S. Patent No. 6,063,820 to Cavazza ("*Cavazza I*"), U.S. Patent No. 6,348,495 to Cavazza et al. ("*Cavazza II*"), U.S. Publication No. 2002/0077349 to Hamilton ("*Hamilton I*"), U.S. Publication No. 2003/0060503 to Hamilton ("*Hamilton II*"), U.S. Patent No. 6,503,506 to Germano ("*Germano*") and U.S. Publication No. 2001/0031774 to Kosbab ("*Kosbab*"). Copies of *De Simone*, *Cavazza I*, *Cavazza II*, *Hamilton I*, *Hamilton II*, *Germano* and *Kosbab* are included in the Evidence Appendix as Exhibits C, D, E, F, G, H and I, respectively.

VII. ARGUMENT

A. LEGAL STANDARDS

Obviousness under 35 U.S.C. § 103

The Federal Circuit has held that the legal determination of an obviousness rejection under 35 U.S.C. § 103 is:

> whether the claimed invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made...The foundational facts for the prima facie case of obviousness are: (1) the scope and content of the prior art; (2) the difference between the prior art and the claimed invention; and (3) the level of ordinary skill in the art...Moreover, objective indicia such as commercial success and long felt need are relevant to the determination of obviousness...Thus, each obviousness determination rests on its own facts.

In re Mayne, 41 U.S.P.Q. 2d 1451, 1453 (Fed. Cir. 1997).

In making this determination, the Patent Office has the initial burden of proving a *prima facie* case of obviousness. *In re Rijckaert*, 28 U.S.P.Q. 2d 1955, 1956 (Fed. Cir. 1993). This burden may only be overcome "by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings." *In re Fine*, 5 U.S.P.Q. 2d 1596, 1598 (Fed. Cir. 1988). "If the examination at the initial stage does not produce a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent." *In re Oetiker*, 24 U.S.P.Q. 2d 1443, 1444 (Fed. Cir. 1992).

Moreover, the Patent Office must provide explicit reasons why the claimed invention is obvious in view of the prior art. The Supreme Court has emphasized that when formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. *KSR v. Teleflex*, 127 S. Ct. 1727 (2007).

Of course, references must be considered as a whole and those portions teaching against or away from the claimed invention must be considered. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve Inc.*, 796 F.2d 443 (Fed. Cir. 1986). "A prior art reference may be considered to teach away when a person of ordinary skill, upon reading the reference would be discouraged

from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the Applicant." *Monarch Knitting Machinery Corp. v. Fukuhara Industrial Trading Co., Ltd.*, 139 F.3d 1009 (Fed. Cir. 1998), quoting, *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994).

B. THE CLAIMED INVENTION

Independent Claim 1 is directed to a method for the stimulation of the lipid metabolism in the skin of an animal or a human being for treating dermatitis. The method includes the step of administering to the animal or human being an ingestible composition comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine. The amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight. and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

Independent Claim 4 is directed to a method for the stimulation of the lipid metabolism in the skin of an animal or a human for preventing the onset or incidence of ulcers associated with diabetes, of circulation disturbances, of physical, chemical or microbial noxae or of eczema. The method includes the steps of administering to a patient at risk of ulcers an ingestible composition comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine. The amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight, and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

Independent Claim 5 is directed to a method for the stimulation of the lipid metabolism in the skin of an animal or a human being for a reduction of itching. The method includes the steps of administering to a patient that is itching due to a skin condition an ingestible composition comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine. The amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight, and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

Independent Claim 6 is directed to a method for making an ingestible composition for the stimulation of the lipid metabolism in the skin of an animal or a human being. The method includes the step of using L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine to

make the composition. The amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight, and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

Independent Claim 18 is directed to an ingestible composition selected from the group consisting of a medicament, a food, a functional food, a nutritional complete pet or human food, and a dietary supplement including L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine. The amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight, and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

C. THE REJECTION OF CLAIMS 1-8, 12-16, 18-21, 31-33, 35-37 AND 39-40 UNDER 35 U.S.C. §103(a) SHOULD BE REVERSED BECAUSE THE EXAMINER HAS FAILED TO ESTABLISH A *PRIMA FACIE* CASE OF OBVIOUSNESS

Appellants respectfully request that the Board reverse the rejection of Claims 1-8, 12-16, 18-21, 31-33, 35-37 and 39-40 under 35 U.S.C. §103(a) because the Examiner has failed to establish a *prima facie* case of obviousness and, even if the Examiner establishes a *prima facie* case of obviousness, Appellants have rebutted the *prima facie* case of obviousness.

1. The Examiner has failed to establish a *prima facie* case of obviousness

Independent Claims 1 and 4-5 recite, in part, a method for the stimulation of the lipid metabolism in the skin of an animal or a human comprising administering an ingestible composition comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine, wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

Independent Claim 6 recites, in part, a method for making an ingestible composition for the stimulation of the lipid metabolism in the skin of an animal or a human being, comprising the step of using L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine to make the composition, wherein the amount of L-carnitine administered daily is from about 1 mg to about 1

g per kg of body weight and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

Independent Claim 18 recites, in part, an ingestible composition selected from the group consisting of a medicament, a food, a functional food, a nutritional complete pet or human food, and a dietary supplement comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine, wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

Conventional methods of improving skin involve the use of topical formulations that merely treat the symptoms of skin conditions, or ingestible compositions which contain rare and expensive starting materials of plant or animal origin. See, specification (WO 2005/074719), page 1, line 19-page 2, line 5. Therefore, the present claims provide an ingestible composition comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine and methods of administering or using the same. The claimed combination of compounds demonstrates a protective activity with respect to inflammatory skin diseases, helps to avoid dermatitis, and increases the lipid secretion in sebum. See, specification, page 5, lines 8-12; page 14, line 1-page 15, line 18; Table 1. In contrast, Appellants respectfully submit that the cited references are deficient with respect to the present claims.

For example, one of ordinary skill in the art would have no reason to combine the teachings of *De Simone*, *Cavazza I*, *Cavazza II*, *Hamilton I*, *Hamilton II*, *Germano* and *Kosbab* to arrive at the present claims. The Examiner asserts that it would have been obvious to one of ordinary skill in the art to combine the teachings of *De Simone*, *Cavazza I*, *Cavazza II*, *Hamilton I*, *Hamilton II*, *Germano* and *Kosbab* to develop non-invasive treatments for various medical problems because the compositions of the cited references also comprise the natural compounds disclosed in the instant claims. See, final Office Action, page 7, lines 5-8. However, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." See, M.P.E.P. §2143.01(III) (2009). Appellants submit that this is not the case with the presently presented claims because the cited references are directed to completely different products having completely different objectives.

For example, *De Simone* is entirely directed to the use of L-acetylcarnitine to induce the production of IGF-1 and treat cytological disorders or diseases related to IGF-1 such as neuropathies of the optic and olfactory nerves, paralysis and osteoporosis. See, *De Simone*, Title; Abstract; column 1, lines 15-34; column 2, lines 44-49. *De Simone* is entirely unconcerned with treating skin disorders or stimulating the lipid metabolism in the skin to increase the lipid secretion in sebum and fails to even mention the terms "skin," "lipid metabolism" or "sebum."

In contrast, *Cavazza I* is directed to a medical food for diabetics comprising γ-linolenic acid and an L-carnitine derivative. See, *Cavazza I*, Title; Abstract; column 2, lines 17-26. *Cavazza I* teaches that its medical food by-passes the enzyme blockade that results in the inadequate conversion of linoleic acid into y-linolenic acid. See, *Cavazza I*, column 2, lines 17-26. *Cavazza II* is directed to the use of alkanoyl L-carnitine to treat inflammatory bowel diseases. See, *Cavazza II*, Title; Abstract; column 1, lines 11-20; column 2, lines 62-67; column 3, lines 1-7. *Cavazza I* and *Cavazza II* are entirely unconcerned with treating skin disorders or stimulating the lipid metabolism in the skin to increase the lipid secretion in sebum.

Hamilton I is directed to the administration of carnitine and lipoid acid to promote healthy mitochondria and treat age-related vision impairment. See, *Hamilton I*, Title; Abstract; page 1, paragraph 2; pages 2-3, paragraph 23. *Hamilton II* is directed to nutritional supplements for mature pets comprising α-lipoic acid and carnitine. See, *Hamilton II*, Title; Abstract; page 1, paragraph 2. In the final Office Action, the Examiner asserts that "the prior art clearly teaches that administration of L-carnitine and antioxidants such as Vitamin C are well known to stimulate lipid metabolism and this is known [to] be beneficial to skin (Hamilton et al., p. 1)." See, final Office Action, page 8, lines 11-13. However, Appellants respectfully disagree and submit that neither *Hamilton I* nor *Hamilton II* teaches what the Examiner alleges. Instead, *Hamilton I* fails to disclose any teaching similar to that alleged by the Examiner. Further, at best, *Hamilton II* discloses that antioxidants such as vitamin C can be used as human nutritional supplements and in dietary prophylaxis and therapy. Indeed, *Hamilton II* merely discloses that lipoic acid can be used in compositions for improving the skin. At no place does *Hamilton I* or *Hamilton II* recognize the benefits obtained by administering the compositions of the present claims.

Germano is entirely directed to a nutritional supplement for treating chronic debilitating diseases such as HIV/AIDS comprising SOD, whey, glutamine, coenzyme Q10 and L-carnitine.

See, *Germano*, Title; Abstract. As such, *Hamilton I*, *Hamilton II* and *Germano* are entirely unconcerned with treating skin disorders or stimulating the lipid metabolism in the skin.

Kosbab is entirely directed to compositions to ameliorate the disease symptoms and conditions associated with vascular and capillary disorders. The compositions may include antioxidants, neovascular regulators, promoters or cofactors involved in collagen synthesis, as well as vitamins and minerals to supplement deficiencies. See, *Kosbab*, Abstract; page 1, paragraph 2. Specifically, *Kosbab* is directed to tissue and cell damage due to oxidative stress and breakdown of collagen in tissues. See, *Kosbab*, page 1, paragraph 9. At best, *Kosbab* discloses the use of L-carnitine among a laundry list of other additives including, for example, butylated hydroxytoluene, ethoxiquin, bioflavins, catchins, angiogenesis regulators, fenugreek, and gymnemic acid, among many others. At no place in the disclosure does *Kosbab* recognize the benefits achieved when the ingredients of the present claims are combined in the presently claimed amounts.

Accordingly, one of ordinary skill in the art would understand that the objectives and anatomical effects resulting from the administration of the compounds of the cited references are entirely distinguishable. As such, one of ordinary skill in the art would have had no reason to combine the teachings of *De Simone*, *Cavazza I*, *Cavazza II*, *Hamilton I*, *Hamilton II*, *Germano* and *Kosbab* to arrive at the present claims with a reasonable expectation of success because the references are directed to different problems in different fields of endeavor.

2. Even if the Examiner has demonstrated a *prima facie* case of obviousness, Appellants have demonstrated unexpected and synergistic results that rebut any *prima facie* case of obviousness

Appellants further submit that even if a prima facie case of obviousness has been established, the present claims are not obvious over the cited references because the specification demonstrates unexpected and synergistic results for the claimed combination of compounds. For example, the specification discloses an experiment in which mice were fed standard Diets A and B consisting of proteins, fat, carbohydrates and cellulose; comparative Diet C consisting of Diet A in addition to vitamin C, vitamin E, grape seed extract and cysteine; Diet D comprising Diet A in addition to L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine; and

comparative Diet E consisting of Diet A and L-carnitine. See, specification, page 12, line 24-page 15, line 18.

Table 1 demonstrates that the incidence of dermatitis in the group of mice fed Diet D including both L-carnitine and vitamin C, vitamin E, grape seed extract and cysteine was 0.00, whereas the incidence of dermatitis in the groups fed standard Diets A and B was 0.10 and 0.11, respectively. See, specification, page 14, Table 1. The incidence of dermatitis in the groups of mice fed Diets C or E including either L-carnitine or vitamin C, vitamin E, grape seed extract and cysteine was 0.16. See, specification, page 14, Table 1. Thus, Table 1 demonstrates that a diet comprising L-carnitine in addition to vitamin C, vitamin E, grape seed extract and cysteine results in a significantly lower incidence of dermatitis compared to diets which do not include the claimed combination. See, specification, page 14, line 1-page 15, line 18; Table 1. As such, the claimed combination of compounds would not have been obvious to one of ordinary skill in the art based on the disclosures of *De Simone*, *Cavazza I*, *Cavazza II*, *Hamilton I*, *Hamilton II*, *Germano* and *Kosbab*.

In the final Office Action, The Examiner states that "[t]he final beneficial effect of the compositions would be expected to be the same whether administered in response to a skin condition or a vision condition or a nutrient uptake condition." See, final Office Action, page 8, lines 3-6. Appellants respectfully disagree in view of the unexpected results set forth in the specification. As discussed above, the specification clearly illustrates that the incidence of dermatitis in the group of mice fed Diet D including both L-carnitine and vitamin C, vitamin E, grape seed extract and cysteine was 0.00, whereas the incidence of dermatitis in the groups fed standard Diets A and B was 0.10 and 0.11, respectively. See, specification, page 14, Table 1. Thus, Table 1 demonstrates that a diet comprising L-carnitine in addition to vitamin C, vitamin E, grape seed extract and cysteine results in a significantly lower incidence of dermatitis compared to diets which do not include the claimed combination. See, specification, page 14, line 1-page 15, line 18; Table 1.

Accordingly, Appellants respectfully request that the rejection of Claims 1-8, 12-16, 18-21, 31-33, 35-37 and 39-40 under 35 U.S.C. §103(a) to *De Simone*, *Cavazza I*, *Cavazza II*, *Hamilton I*, *Hamilton II*, *Germano* and *Kosbab* be reconsidered and withdrawn.

VIII. CONCLUSION

Appellants respectfully submit that the Examiner has failed to establish obviousness under 35 U.S.C. §103 with respect to Claims 1-8, 12-16, 18-21, 31-33, 35-37 and 39-40 and that, even if the Examiner has established a *prima facie* case of obviousness, Appellants have rebutted any showing of obviousness by demonstrating surprising and unexpected results. Accordingly, Appellants respectfully submit that the obviousness rejection is erroneous in law and in fact and should, therefore, be reversed by this Board.

The Director is authorized to charge $540 for the Appeal Brief and any additional fees which may be required, or to credit any overpayment to Deposit Account No. 02-1818. If such a withdrawal is made, please indicate the Attorney Docket No. 3712036-00745 on the account statement.

Respectfully submitted,

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Dated: October 27, 2010

CLAIMS APPENDIX

PENDING CLAIMS ON APPEAL OF U.S. PATENT APPLICATION SERIAL NO. 10/597,436

1. A method for the stimulation of the lipid metabolism in the skin of an animal or a human being for treating dermatitis comprising administering an ingestible composition comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine, wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

2. The method according to claim 1, wherein the composition increases the lipid secretion in the sebum and/or for producing a protective sebum layer on the skin.

3. The method according to claim 1, wherein the patient has ulcerative dermatitis.

4. A method for the stimulation of the lipid metabolism in the skin of an animal or a human for preventing the onset or incidence of ulcers associated with diabetes, of circulation disturbances, of physical, chemical or microbial noxae or of eczema, comprising the steps of administering to a patient at risk of ulcers an ingestible composition comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine, wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

5. A method for the stimulation of the lipid metabolism in the skin of an animal or a human being for a reduction of itching comprising the steps of administering to a patient that is itching due to a skin condition an ingestible composition comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine, wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

6. A method for making an ingestible composition for the stimulation of the lipid metabolism in the skin of an animal or a human being, comprising the step of using L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine to make the composition, wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

7. The method according to claim 6, for producing a protective sebum layer on the skin.

8. The method according to claim 6 for reducing dry skin or itching.

12. The method according to claim 1, wherein the ingestable composition contains a source of fat.

13. The method according to claim 12, wherein the fat comprises alpha-linolenic acid.

14. The method according to claim 12, wherein said source of fat is selected from the group consisting of an animal fat, a vegetable fat, and combinations thereof.

15. The method according to claim 12, wherein the amount of said source of fat in the composition is at least 0.1 % by weight on basis of the total weight of the composition.

16. The method according to claim 1, wherein the ingestable composition is selected from the group consisting of a medicament, a food, a functional food, a nutritionally complete pet or human food, a dietary supplement, and combinations thereof.

18. An ingestible composition selected from the group consisting of a medicament, a food, a functional food, a nutritional complete pet or human food, and a dietary supplement comprising L-carnitine, vitamin C, vitamin E, grape seed extract and cysteine, wherein the amount of L-carnitine administered daily is from about 1 mg to about 1 g per kg of body weight and the amount of vitamin C administered daily is from about 0.025 mg to about 250 mg per kg of body weight.

19. The method according to claim 4, the ingestible composition further comprising a component exhibiting an anti-oxidative activity selected from the group consisting of: carotenoids; ubiquinones; tea catechins; coffee extracts containing polyphenols and/or diterpenes; ginkgo biloba extracts; spice extracts; soy extracts containing isoflavones, phytoestrogens; ursodeoxycholic acid; ursolic acid; ginseng and gingenosides and natural sources thereof; a source of thiols, preferably lipoic acid, cystine, methionine, S-adenosyl-methionine, taurine, glutathione or natural sources thereof; and combinations thereof.

20. The method according to claim 5, the ingestible composition further comprising a component exhibiting an anti-oxidative activity selected from the group consisting of: carotenoids; ubiquinones; tea catechins; coffee extracts containing polyphenols and/or diterpenes; ginkgo biloba extracts; spice extracts; soy extracts containing isoflavones, phytoestrogens; ursodeoxycholic acid; ursolic acid; ginseng and gingenosides and natural sources thereof; a source of thiols, preferably lipoic acid, cystine, methionine, S-adenosyl-methionine, taurine, glutathione or natural sources thereof; and combinations thereof.

21. The method according to claim 6, the method further comprising using an additional component to make the composition, the additional component exhibiting an anti-oxidative activity is selected from the group consisting of vitamin E; carotenoids; ubiquinones; tea catechins; coffee extracts containing polyphenols and/or diterpenes; ginkgo biloba extracts; grape or grape seed extracts rich in proanthocyanidins; spice extracts; soy extracts containing isoflavones, phytoestrogens; ursodeoxycholic acid; ursolic acid; ginseng and gingenosides and natural sources thereof; a source of thiols, preferably lipoic acid, cysteine, cystine, methionine, S-adenosyl-methionine, taurine, glutathione or natural sources thereof; and combinations thereof.

31. The method according to claim 4, wherein the ingestable composition contains a source of fat.

32. The method according to claim 5, wherein the ingestable composition contains a source of fat.

33. The method according to claim 6, wherein the ingestable composition contains a source of fat.

35. The method according to claim 4, wherein the ingestable composition is selected from the group consisting of a medicament, a food, a functional food, a nutritionally complete pet or human food, a dietary supplement, and combinations thereof.

36. The method according to claim 5, wherein the ingestable composition is selected from the group consisting of a medicament, a food, a functional food, a nutritionally complete pet or human food, a dietary supplement, and combinations thereof.

37. The method according to claim 6, wherein the ingestable composition is selected from the group consisting of a medicament, a food, a functional food, a nutritionally complete pet or human food, a dietary supplement, and combinations thereof.

39. The method according to claim 1, the ingestible composition further comprising a component having anti-oxidative activity selected from the group consisting of: carotenoids; ubiquinones; tea catechins; coffee extracts containing polyphenols and/or diterpenes; ginkgo biloba extracts; spice extracts; soy extracts containing isoflavones, phytoestrogens; ursodeoxycholic acid; ursolic acid; ginseng and gingenosides and natural sources thereof; a source of thiols, preferably lipoic acid, cystine, methionine, S-adenosyl-methionine, taurine, glutathione or natural sources thereof; and combinations thereof; said ingestable composition selected from the group consisting of a food or a functional food, a nutritionally complete pet or human food, a dietary supplement, and combinations thereof.

40. The ingestible composition according to claim 18, the composition further including a component having an anti-oxidative activity and being selected from the group consisting of ubiquinones; tea catechins; coffee extracts containing polyphenols and/or diterpenes; ginkgo biloba extracts; spice extracts; soy extracts containing isoflavones, phytoestrogens; ursodeoxycholic acid; ursolic acid; ginseng and gingenosides and natural sources thereof; cystine, methionine, S-adenosyl-methionine, taurine or natural sources thereof; and combinations thereof.

EVIDENCE APPENDIX

EXHIBIT A: Non-Final Office Action dated December 30, 2009

EXHIBIT B: Final Office Action dated June 29, 2010

EXHIBIT C: U.S. Patent No. 6,380,252 to De Simone ("*De Simone*")

EXHIBIT D: U.S. Patent No. 6,063,820 to Cavazza ("*Cavazza I*")

EXHIBIT E: U.S. Patent No. 6,348,495 to Cavazza et al. ("*Cavazza II*")

EXHIBIT F: U.S. Publication No. 2002/0077349 to Hamilton ("*Hamilton I*")

EXHIBIT G: U.S. Publication No. 2003/0060503 to Hamilton ("*Hamilton II*")

EXHIBIT H: U.S. Patent No. 6,503,506 to Germano ("*Germano*")

EXHIBIT I: U.S. Publication No. 2001/0031774 to Kosbab ("*Kosbab*")

RELATED PROCEEDINGS APPENDIX

None.

EXHIBIT A

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,436	08/22/2008	Sylvie Pridmore-Merten	112701-745	1948

29157 7590 12/30/2009

K&L Gates LLP
P.O. Box 1135
CHICAGO, IL 60690

EXAMINER	
HOBBS, LISA JOE	
ART UNIT	PAPER NUMBER
1657	

NOTIFICATION DATE	DELIVERY MODE
12/30/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chicago.patents@klgates.com

Office Action Summary	Application No.	Applicant(s)	
	10/597,436	PRIDMORE-MERTEN, SYLVIE	
	Examiner	Art Unit	
	Lisa J. Hobbs	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

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- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,12-21,31-33,35-37,39 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12-21,31-33,35-37,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

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3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02 October 2009 has been entered.

Claim Status

Claims 1-8, 12-21, 31-33, 35-37, 39-40 are active in the case. Claims 1-8, 12-21, 31-33, 35-37, 39-40 are under examination; no claims are withdrawn as drawn to a non-elected invention. Claims 9-11, 22-30, 34 and 38 have been cancelled by amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8, 12-21, 31-33, 35-37, 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Simone (US 6,380,252 A), Cavazza (US 6,063,820 A and 6,348,495 A), Hamilton (US 2002/ 077349 A and 2003/060503 A), and Germano (US 6,503,506 A).

De Simone teaches "[a] method is provided for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1 selected from the group including neuropathies of the optic nerve and of the olfactory nerve, neuralgia of the trigmeninal nerve, Bell's paralysis, amyotrophic lateral sclerosis, osteoporosis, anthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs clinical syndromes of reduced height, cachexia and acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensitivity syndromes, obesity, asthenia, myasthenia and heart asthenia, immunodeficiences and reperfusion injuries, and for the cicatrization of wounds, the healing of ulcers, the treatment of burns, tissue regeneration, cutaneous, intestinal and hepatic tissue regeneration and the formation of dentine, that includes administering, to a patient in need thereof, at least one selected from the group including L-acetylcarnitine, L-isovalerylcarnitine, and L-propionylcarnitine or pharmacologically acceptable salts thereof. The present invention also relates to a method and composition for treating HCV and/or increasing the levels of IGF-1 of a patient in need thereof, the composition including at least one selected from the group including L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine and pharmacologically acceptable salts thereof and mixtures thereof; and at least one selected from the group including

L -carnitine, coenzyme Q10, vitamin E and Se-L-methionine and pharmaceutically acceptable salts and derivatives thereof and mixtures thereof" (abstract).

Cavazza ('495) teaches "[a] medical food for diabetics is disclosed which comprises as characterizing active ingredients .gamma.-linolenic acid and at least one alkanoyl-L -carnitine, e.g. acetyl-L -carnitine and/or propionyl-L –carnitine" (abstract) and that "[a]n object of the present invention is to provide a medical food for diabetics which enables them to compensate for the reduced metabolism of essential fatty acids typical of such subjects. In particular, the object of the present invention is to provide a medical food of this type which makes it possible to by-pass the enzyme blockade caused by the reduced activity of omega-6-desaturase which occurs in diabetics and gives rise to inadequate conversion of linoleic acid into y-linolenic acid and thus to a reduced production of prostaglandin and leukotriene precursors (BSUM paragraph 17). Also taught (Cavazza '820) is "a new therapeutic use of the lower alkanoyl L-carnitines and their pharmacologically acceptable salts to produce pharmaceutical compositions for the treatment of chronic intestinal disorders, in particular inflammatory bowel diseases, more particularly, ulcerative colitis or celiac disease" (BSUM paragraph 1).

Cavazza ('495) teaches at Example 2: "S.C., male, 20 years old, height 178 cm, weight 69 Kg. Regularly born, he was breast-fed by her mother for about 40 days. At about 9 months diarrhoea and meteorism appeared, lasting one month. Regular growth and sexual development. Measles. In 1995 a blister dermatitis appeared, with strong itching. After different hypotheses, a Duhring dermatitis was diagnosed. An EGDS was carried out with biopsies reporting celiac disease. A rigid gluten-free diet started. Dermatitis was resolved, but still 2-3 daily discharges, with poorly formed faeces and abdominal pains were reported. The patient started the treatment

with propionyl L -carnitine (2 grams/day orally for two months), with an improvement of the general symptomatology. After 4 months the patient started sporting activity again".

Hamilton (2002) teaches "methods to treat age-related vision losses. The method comprises administering a combination of a carnitine and an oxidant. Preferably the oxidant is thioctic acid. Preferably 0.12 grams to 3 grams of carnitine (particularly ALC) and 0.12 and 1.5 grams of R-.alpha.-lipoic acid are administered. Optionally, coenzyme Q and/or creatine also are administered. Preferably 10 mg to 500 mg/day of coenzyme Q10 and 1 to 30 grams/day of creatine are administered" (abstract). As well, Hamilton also teaches (2003) "compositions to meet the needs of aged pets and other animals. A pet food formulated for senior pets provides .alpha.-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day. A pet treat for senior pets provides .alpha.-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day. A pet supplement for mature pets offers .alpha.-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day" (abstract).

Germano teaches "[a] nutritional supplement...for treating chronic debilitating diseases such as HIV/AIDS to overcome conditions of oxidative stress, decreased lean muscle mass, decreased energy production (mitochondrial failure) and support immune function. It comprises orally administrable superoxide dismutase (SOD), preferably SOD/GLIADIN, in combination with other antioxidant/immune support components (Beta Glucans, Nucleotides, Fruit

Polyphenols); High Immunoglobin Whey; (undenatured whey), Ornithine alpha ketoglutarate (OKG), Branched Chain Amino Acids and Glutamine to reduce loss of lean muscle mass; and Coenzyme Q 10, D-Ribose and L-Carnitine to provide energy support (decrease mitochondrial failure).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of De Simone, Cavazza, Hamilton, and Germano to achieve the invention as recited. One would be motivated to do so in order to develop non-invasive treatments, especially treatments that would be part of a daily schedule such as food, for various medical problems as outlined in the prior art. One would have a reasonable expectation of success since the medically oriented foodstuffs and compositions taught also comprise the natural compounds, such as isoprenoids, terpenes, ginkgo biloba, etc., disclosed in the instant claims.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicants argue that each of the references does not teach the invention as currently recited in the claims. However, when taken as a whole, the references clearly teach the medicinal use of L-carnitine when administered in conjunction with anti-oxidants and other medicinal and nutriceutical elements in the ranges recited in the claims. Applicants particularly argue that the prior art does not teach the administration of the compounds as recited in the claims, that the prior art references teach completely unrelated products having completely unrelated objectives. However, it is noted that the objectives of the administration of the compounds is presented in the preambles to the instant claims, which are given limited weight and consideration when

determining patentability. The actual method step, administration of L-carnitine and anti-oxidant compositions to animals or humans in need thereof is clearly taught in the cited prior art at the levels recited in the claims. The final beneficial effect of the compositions would be expected to be the same whether administered in response to a skin condition or a vision condition or a nutrient uptake condition.

Applicants state that the prior art does not teach a combination of L – carnitine with Vitamin C at the levels recited in the claims, however the prior art teaches carnitine and Vitamin C at many dosage amounts, comprising and encompassing the large dosage range recited by applicants. Applicants argue that the prior art recited would not be applied to the instant diseases, however the prior art clearly teaches that administration of L-carnitine and antioxidants such as Vitamin C are well known to stimulate lipid metabolism and this is known be beneficial to skin (Hamilton et al., p. 1). Applicants argue that one of skill wouldn't use references that are directed at amelioration of other medical conditions, however the skilled artisan is aware that such compositions and administration of them is beneficial to the patient's lipid metabolism pathways and the final medical application is not as pertinent as the fact that L-carnitine and antioxidants, such as Vitamin C, are known to beneficially affect lipid metabolism. Indeed, applicant supports this by having groups of claims to medicaments and dietary supplements for human application and animal application, as well as methods of administration, all relating to changing lipid metabolism, as is taught in the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa J. Hobbs whose telephone number is 571-272-3373. The examiner can normally be reached on Hotelling - Generally, 9-6 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lisa J. Hobbs/
Primary Examiner
Art Unit 1657

ljh

EXHIBIT B

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,436	08/22/2008	Sylvie Pridmore-Merten	3712036.00745	1948

29157 7590 06/29/2010

K&L Gates LLP
P.O. Box 1135
CHICAGO, IL 60690

EXAMINER	
HOBBS, LISA JOE	

ART UNIT	PAPER NUMBER
1657	

NOTIFICATION DATE	DELIVERY MODE
06/29/2010	ELECTRONIC

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chicago.patents@klgates.com

Office Action Summary	Application No.	Applicant(s)	
	10/597,436	PRIDMORE-MERTEN, SYLVIE	
	Examiner	Art Unit	
	Lisa J. Hobbs	1657	

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Status

1)☒ Responsive to communication(s) filed on *30 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-16,18-21,31-33,35-37,39 and 40* is/are pending in the application.

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8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

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10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

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a)☒ All b)☐ Some * c)☐ None of:

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DETAILED ACTION

Claim Status

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Claims 1-8, 12-16, 18-21, 31-33, 35-37, 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Simone (US 6,380,252 A), Cavazza (US 6,063,820 A and 6,348,495 A), Hamilton (US 2002/ 077349 A and 2003/060503 A), Germano (US 6,503,506 A), and Kosbab (US 2001/0031744 A1).

De Simone teaches "[a] method is provided for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1 selected from the group including neuropathies of the optic nerve and of the olfactory nerve, neuralgia of the trigmeninal nerve, Bell's paralysis, amyotrophic lateral sclerosis, osteoporosis, anthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs clinical syndromes of reduced height, cachexia and acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensitivity syndromes, obesity, asthenia, myasthenia and heart asthenia, immunodeficiences and reperfusion injuries, and for the cicatrization of wounds, the healing of ulcers, the treatment of burns, tissue regeneration, cutaneous, intestinal and hepatic tissue regeneration and the formation of dentine, that includes administering, to a patient in need thereof, at least one selected from the group including L-acetylcarnitine, L-isovalerylcarnitine, and L-propionylcarnitine or pharmacologically acceptable salts thereof. The present invention also relates to a method and composition for treating HCV and/or increasing the levels of IGF-1 of a patient in need thereof, the composition including at least one selected from the group including L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine and pharmacologically acceptable salts thereof and mixtures thereof; and at least one selected from the group including L -carnitine, coenzyme Q10, vitamin E and Se-L-methionine and pharmaceutically acceptable salts and derivatives thereof and mixtures thereof" (abstract).

Cavazza ('495) teaches "[a] medical food for diabetics is disclosed which comprises as characterizing active ingredients .gamma.-linolenic acid and at least one alkanoyl-L -carnitine, e.g. acetyl-L -carnitine and/or propionyl-L –carnitine" (abstract) and that "[a]n object of the present invention is to provide a medical food for diabetics which enables them to compensate

for the reduced metabolism of essential fatty acids typical of such subjects. In particular, the object of the present invention is to provide a medical food of this type which makes it possible to by-pass the enzyme blockade caused by the reduced activity of omega-6-desaturase which occurs in diabetics and gives rise to inadequate conversion of linoleic acid into y-linolenic acid and thus to a reduced production of prostaglandin and leukotriene precursors (BSUM paragraph 17). Also taught (Cavazza '820) is "a new therapeutic use of the lower alkanoyl L-carnitines and their pharmacologically acceptable salts to produce pharmaceutical compositions for the treatment of chronic intestinal disorders, in particular inflammatory bowel diseases, more particularly, ulcerative colitis or celiac disease" (BSUM paragraph 1).

Cavazza ('495) teaches at Example 2: "S.C., male, 20 years old, height 178 cm, weight 69 Kg. Regularly born, he was breast-fed by her mother for about 40 days. At about 9 months diarrhoea and meteorism appeared, lasting one month. Regular growth and sexual development. Measles. In 1995 a blister dermatitis appeared, with strong itching. After different hypotheses, a Duhring dermatitis was diagnosed. An EGDS was carried out with biopsies reporting celiac disease. A rigid gluten-free diet started. Dermatitis was resolved, but still 2-3 daily discharges, with poorly formed faeces and abdominal pains were reported. The patient started the treatment with propionyl L -carnitine (2 grams/day orally for two months), with an improvement of the general symptomatology. After 4 months the patient started sporting activity again".

Hamilton (2002) teaches "methods to treat age-related vision losses. The method comprises administering a combination of a carnitine and an oxidant. Preferably the oxidant is thioctic acid. Preferably 0.12 grams to 3 grams of carnitine (particularly ALC) and 0.12 and 1.5 grams of R-.alpha.-lipoic acid are administered. Optionally, coenzyme Q and/or creatine also are

administered. Preferably 10 mg to 500 mg/day of coenzyme Q10 and 1 to 30 grams/day of creatine are administered" (abstract). As well, Hamilton also teaches (2003) "compositions to meet the needs of aged pets and other animals. A pet food formulated for senior pets provides .alpha.-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day. A pet treat for senior pets provides .alpha.-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day. A pet supplement for mature pets offers .alpha.-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day" (abstract).

Germano teaches "[a] nutritional supplement...for treating chronic debilitating diseases such as HIV/AIDS to overcome conditions of oxidative stress, decreased lean muscle mass, decreased energy production (mitochondrial failure) and support immune function. It comprises orally administrable superoxide dismutase (SOD), preferably SOD/GLIADIN, in combination with other antioxidant/immune support components (Beta Glucans, Nucleotides, Fruit Polyphenols); High Immunoglobin Whey; (undenatured whey), Ornithine alpha ketoglutarate (OKG), Branched Chain Amino Acids and Glutamine to reduce loss of lean muscle mass; and Coenzyme Q 10, D-Ribose and L-Carnitine to provide energy support (decrease mitochondrial failure).

Kosbab teaches "nutrient and therapeutic compositions for treatment and prevention of symptoms and disease conditions associated with microangiopathy and macroangiopathy and to

methods using the compositions. In particular, the invention relates to compositions useful in the treatment of diabetic retinopathy and nephropathy, to compositions useful in the treatment of other retinal disorders including macular degeneration and cataracts, to compositions useful in wound healing, to compositions useful for treatment and prevention of neuropathy, to compositions useful for treatment and prevention of cardiovascular disease and to compositions useful for the treatment and prevention of dental and periodontal disorders" and that "[v]ascular degeneration is directly associated with cardiovascular disease, atherosclerosis and plaque deposition and indirectly associated with degenerative conditions of the retina (including retinopathy), kidney (nephropathy) and nervous system (neuropathy), as well as skin ulcers" [0003].

He also teaches that "L -Carnitine is an essential co-factor of fatty acid metabolism. Significantly decreased plasma carnitine levels are common in insulin dependent diabetics including those with nephropathies. This implies that such patients may suffer from inadequate ATP reserves that could cause fatigue and oxidative stress due to reduced lipid metabolism caused by faulty transport of fatty acids across mitochondrial membranes. Carnitine supplementation supports increases in fat utilization and oxygen uptake while decreasing plasma lactate levels and respiratory quotients. Carnitine has been shown to reduce ketones, LDL and triglycerides and increase HDL while acting as a vasodilator. Low carnitine levels may correlate with low plasma albumin and edema. L -Carnitine can be provided as N-acetyl-l -carnitine hydrochloride, the preferred form for this invention. Carnitine can be also be provided as the 1- or d,1-form as hydrochloride or other salts" [0453].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of De Simone, Cavazza, Hamilton, Germano and Kosbab to achieve the invention as recited. One would be motivated to do so in order to develop non-invasive treatments, especially treatments that would be part of a daily schedule such as food, for various medical problems as outlined in the prior art. One would have a reasonable expectation of success since the medically oriented foodstuffs and compositions taught also comprise the natural compounds, such as isoprenoids, terpenes, ginkgo biloba, etc., disclosed in the instant claims.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicants argue that each of the references does not teach the invention as currently recited in the claims. However, when taken as a whole, the references clearly teach the medicinal use of L-carnitine when administered in conjunction with anti-oxidants and other medicinal and nutriceutical elements in the ranges recited in the claims. Applicants particularly argue that the prior art does not teach the administration of the compounds as recited in the claims, that the prior art references teach completely unrelated products having completely unrelated objectives. However, it is noted that the objectives of the administration of the compounds is presented in the preambles to the instant claims, which are given limited weight and consideration when determining patentability. However, it is noted that Kosbab specifically states that L-carnitine administered to a subject may assist with lipid metabolism and that skin disorders are contemplated as within the metes and bounds of his treatment methods.

The actual method step, administration of L-carnitine and anti-oxidant compositions to animals or humans in need thereof is clearly taught in the cited prior art at the levels recited in the claims. The final beneficial effect of the compositions would be expected to be the same whether administered in response to a skin condition or a vision condition or a nutrient uptake condition. Kosbab does specifically state that L-carnitine may assist a subject with lipid metabolism problems.

Applicants state that the prior art does not teach a combination of L – carnitine with Vitamins C and E, and grape seed extract at the levels recited in the claims, however the prior art teaches the recited components at many dosage amounts, comprising and encompassing the large dosage range recited by applicants. Applicants argue that the prior art recited would not be applied to the instant diseases, however the prior art clearly teaches that administration of L-carnitine and antioxidants such as Vitamin C are well known to stimulate lipid metabolism and this is known be beneficial to skin (Hamilton et al., p. 1). Applicants argue that one of skill wouldn't use references that are directed at amelioration of other medical conditions, however the skilled artisan is aware that such compositions and administration of them is beneficial to the patient's lipid metabolism pathways and the final medical application is not as pertinent as the fact that L-carnitine and antioxidants, such as Vitamin C, are known to affect lipid metabolism in a positive manner. Indeed, applicant supports this by having groups of claims to medicaments and dietary supplements for human application and animal application, as well as methods of administration, all relating to changing lipid metabolism, as is taught in the prior art.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa J. Hobbs whose telephone number is 571-272-3373. The examiner can normally be reached on Hotelling - Generally, 9-6 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lisa J. Hobbs/
Primary Examiner
Art Unit 1657

ljh

Notice of References Cited	Application/Control No. 10/597,436	Applicant(s)/Patent Under Reexamination PRIDMORE-MERTEN, SYLVIE	
	Examiner Lisa J. Hobbs	Art Unit 1657	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2001/0031744	10-2001	Kosbab, John V.	514/54
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EXHIBIT C

US006380252B1

(12) **United States Patent**
De Simone

(10) **Patent No.: US 6,380,252 B1**
(45) **Date of Patent: Apr. 30, 2002**

(54) **USE OF L-ACETYLCARNITINE, L-ISOVALERYLCARNITINE, L-PROPIONYLCARNITINE FOR INCREASING THE LEVELS OF IGF-1**

(75) Inventor: **Claudio De Simone**, Ardrea (IT)

(73) Assignees: **Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.**, Rome; **Mendes S.R.L.**, Ardea, both of (IT)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/510,669**

(22) Filed: **Feb. 22, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/510,672, filed on Feb. 22, 2000, now Pat. No. 6,166,077, which is a continuation of application No. 09/147,465, filed as application No. PCT/IT97/00113 on May 15, 1997, now Pat. No. 6,037,373.

(51) **Int. Cl.**[7] **A61K 31/205**

(52) **U.S. Cl.** **514/556**; 424/400; 424/489; 514/228.8

(58) **Field of Search** 514/556, 228.8

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,166,077 A * 12/2000 De Simone 514/556

* cited by examiner

Primary Examiner—Thurman K. Page
Assistant Examiner—Charesse L. Evans
(74) *Attorney, Agent, or Firm*—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

(57) **ABSTRACT**

A method is provided for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1 selected from the group including neuropathies of the optic nerve and of the olfactory nerve, neuralgia of the trigmeninal nerve, Bell's paralysis, amyotrophic lateral sclerosis, osteoporosis, anthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs clinical syndromes of reduced height, cachexia and acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensitivity syndromes, obesity, asthenia, myasthenia and heart asthenia, immunodeficiences and reperfusion injuries, and for the cicatrization of wounds, the healing of ulcers, the treatment of burns, tissue regeneration, cutaneous, intestinal and hepatic tissue regeneration and the formation of dentine, that includes administering, to a patient in need thereof, at least one selected from the group including L-acetylcarnitine, L-isovalerylcarnitine, and L-propionylcarnitine or pharmacologically acceptable salts thereof. The present invention also relates to a method and composition for treating HCV and/or increasing the levels of IGF-1 of a patient in need thereof, the composition including at least one selected from the group including L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine and pharmacologically acceptable salts thereof and mixtures thereof; and at least one selected from the group including L-carnitine, coenzyme Q10, vitamin E and Se-L-methionine and pharmaceutically acceptable salts and derivatives thereof and mixtures thereof.

20 Claims, No Drawings

USE OF L-ACETYLCARNITINE, L-ISOVALERYLCARNITINE, L-PROPIONYLCARNITINE FOR INCREASING THE LEVELS OF IGF-1

This application is a continuation-in-part of U.S. patent application Ser. No. 09/510,672, filed Feb. 22, 2000, now U.S. Pat. No. 6,166,077, which is a continuation of U.S. patent application Ser. No. 09/147,465, filed as national stage application no. PCT/IT97/00113 on May 15, 1997, now U.S. Pat. No. 6,037,373.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a novel therapeutic use of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof for increasing the levels of IGF-1 (insulin-like growth factor 1) for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1. More particularly, the present invention relates to the use of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof for the therapeutic treatment or prophylaxis of individuals in whom IGF-1 contributes towards the pathogenesis of a particular disease or provokes cytological disorders. The present invention also relates to the use of any of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof in combination with any of L-carnitine, coenzyme Q10, vitamin E and/or Se-L-methionine and pharmaceutically acceptable salts and derivatives thereof in the treatment of hepatitis-C virus and/or for increasing the levels of IGF-1.

Like other growth factors, IGF-1 promotes cell growth and differentiation. The administration of IGF-1 obtained as a protein purified by molecular biology methods has made it possible to confirm the effects observed in vitro with cells, on animal models and in man. Essentially, the action of IGF-1 is similar to that of insulin, that is to say an increase in the uptake of glucose, a reduction in ketones and fatty acids in the serum and an increase in protein synthesis. In accordance with these and other metabolic effects, clinical studies have been undertaken in order to evaluate the efficacy of IGF-1 in a range of diseases. IGF-1 has been administered to patients with type-II diabetes, to cachectic patients, to patients with ischemic damage at the neuronal, myocardial or renal level, and has been proposed for repairing and regenerating tissues (W. L. Lowe, Insulin-like growth factors, Scientific American Science and Medicine p. 62, March 1996).

From the above, it is clear that the administration of IGF-1 may be therapeutically useful in various morbid conditions. Examples of diseases or disorders which may be prevented, cured or improved by the administration of IGF-1 include neuropathies of the optic nerve and of the olfactory nerve, neuralgia of the trigeminal nerve, Bell's paralysis, amyotrophic lateral sclerosis and other motor neuron diseases, degeneration of the retina, osteoporosis, arthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs, clinical syndromes of reduced height, cachexia, acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensitivity syndromes, diabetes, obesity, asthenia in general and in particular myasthenia and heart asthenia, immunodeficiencies and reperfusion injuries. IGF-1 moreover appears to be useful for the cicatrization of wounds, the healing of ulcers, the treatment

of burns, tissue regeneration in general and in particular that of cutaneous, intestinal and hepatic tissue, and the formation of dentine.

Unfortunately, the administration of IGF-1 in man brings about undesirable effects such as oedema, pain in the temporomandibular joint and arthralgia. These symptoms are such as to prevent the administration of IGF-1 from being recommended or are responsible for interrupting the treatment. It is therefore necessary to find novel substances which are capable of inducing the production of IGF-1.

In addition, hepatitis C virus (HCV) is the most common cause of viral hepatitis in the developed world. In some populations of the Middle East the incidence of antibodies against HCV peaks up to 6%. Despite many advances in the knowledge of HCV, the pathogenesis of this infection is still not characterized in all its aspects. In particular, it is not presently known how HCV causes hepatic cell injury; the histological findings of the livers of HCV-infected patients revealing a variety of complex interactions between host and viral factors. The most striking observation at the ultrastructural level is the severe alteration in the mitochondria of hepatocytes from patients who are HCV-infected. The dysfunction of the mitochondria leads to the promotion of both immune- and non-immune-mediated death of the hepatocyte. In chronic HCV infection, this sequence of events leads to chronic hepatic necrosis and finally even to cirrhosis in advanced disease.

Even though the "standard" treatment of HCV-infected patients is based on the use of interferons—mainly alpha-IFN (α-IFN), eventually in association with other antivirals (i.e. ribavirin), the inventors surprisingly found that compositions that contain any of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof in combination with any of L-carnitine, coenzyme Q10, Vitamin E and/or Se-L-Methionine and pharmaceutically acceptable salts and derivatives thereof can lead to new therapeutic strategies for HCV treatment as well as other conditions where IGF-1 levels are deficient and which lead to increased and/or prolonged cell death (i.e. HIV-infection, retinal damage, and also those noted above). This formulation can be given as dietary supplement or as a drug.

According to one embodiment of the present invention, the administration of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof is capable of inducing the production of IGF-1 without the undesirable effects produced by the administration of exogenous IGF-1.

According to another embodiment of the present invention, the administration of any of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof in combination with any of L-carnitine, coenzyme Q10, vitamin E and/or Se-L-methionine and pharmaceutically acceptable salts and derivatives thereof can lead to new therapeutic strategies for HCV treatment as well as other conditions where IGF-1 levels are deficient.

In the description which follows, the expression pharmacologically acceptable salt of L-acetylcarnitine, of L-isovalerylcarnitine or of L-propionylcarnitine is understood to refer to any salt of the above with an acid which does not give rise to undesirable toxicity or side-effects. Such acids are well known to pharmacologists and to experts in the pharmaceutical field.

Non-limiting examples of such salts are; chloride; bromide; iodide; aspartate, in particular hydrogen aspartate;

citrate, in particular hydrogen citrate; tartrate; phosphate, in particular hydrogen phosphate; fumarate, in particular hydrogen fumarate; glycerophosphate, glucose phosphate; lactate; maleate, in particular hydrogen maleate; orotate; oxalate, in particular hydrogen oxalate; sulphate, in particular hydrogen sulphate; trichloroacetate, trifluoroacetate and methanesulphonate.

In the description which follows, for the purposes of brevity and for ease of explanation, reference will be made only to L-acetylcarnitine, it being understood that the description given applies also to the above-mentioned L-isovalerylcarnitine and L-propionylcarnitine and to pharmacologically acceptable salts thereof.

Therapeutic uses of L-acetylcarnitine, L-isovalerylcarnitine and L-propionylcarnitine for the therapeutic treatment of myocardial arrhythmia and ischemia, peripheral functional vasculopathy of the arteries, senile dementia, peripheral neuropathies and myopathies are already previously known. For instance, EP 0 516 594 A1, the entire contents of which are hereby incorporated by reference, discloses the use of propionyl- and isovaleryl L-carnitine for treating myopathies, neuronal degeneration and for inhibiting proteolysis. Cardiov. Res. 1986, 20:536–541, the entire contents of which are hereby incorporated by reference, deals with the protection of the ischaemic myocardium by propionyl L-carnitine. Docum. Ophtal. 1988, 70:89–96, the entire contents of which are hereby incorporated by reference, hints at therapeutic potentialities of acetyl L-carnitine in diabetes and diabetic complications of the visual system. However, there is no correlation between these known therapeutic uses and the subject of the present invention.

It has now been found, surprisingly, that L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmaceutically acceptable salts thereof are capable of increasing the levels of IGF-1 in human biological fluids. It should be emphasized that, on the basis of extensive supporting scientific literature, the mechanism of action of L-acetylcarnitine has been focused at the metabolic level, more specifically demonstrating a protective action with respect to the mitochondria, whereas the present invention demonstrates an action mediated by the production of IGF-1.

In one embodiment of the present invention, the L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmaceutically acceptable salts thereof are administered in combination with vasodilatory, vascular, endocrinological, immunological, cytostatic, immunomodulatory, anti-inflammatory or cortisone pharmaceutical products, IGF-1, IGF-1 binding proteins, growth hormones and other cell growth factors such as, for example, epidermal growth factor, and erythropoietin.

According to another embodiment of the present invention, the administration of any of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof in combination with any of L-carnitine, coenzyme Q10, vitamin E and/or Se-L-methionine and pharmaceutically acceptable salts and derivatives thereof can lead to new therapeutic strategies for HCV treatment as well as other conditions where IGF-1 levels are deficient.

Various preferred embodiments of the invention, A–M, which are not intended to be limiting, are listed below.

A. A method for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1 selected from the group consisting of neuropathies of the optic nerve and of the olfactory nerve, neuralgia of the trigeminal nerve, Bell's paralysis, amyotrophic lateral sclerosis and other motor neuron diseases, degeneration of the retina, osteoporosis, arthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs, clinical syndromes of reduced height, cachexia and acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensitivity syndromes, diabetes, obesity, asthenia in general and in particular myasthenia and heart asthenia, immunodeficiencies and reperfusion injuries, and for the cicatrization of wounds, the healing of ulcers, the treatment of burns, tissue regeneration in general and in particular that of cutaneous, intestinal and hepatic tissue, and the formation of dentine, that includes:

administering, to a patient in need thereof, at least one selected from the group consisting of L-acetylcarnitine, L-isovalerylcarnitine, and L-propionylcarnitine or pharmacologically acceptable salts thereof.

B. The method of A, in which the L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof are administered in combination with at least one selected from the group consisting of vasodilatory, vascular, endocrinological, immunological, cytostatic, immunomodulatory, anti-inflammatory or cortisone pharmaceutical products, IGF-1, IGF-1 binding proteins, growth hormones and epidermal growth factor, and erythropoietin.

C. The method of A, in which L-acetylcarnitine is administered.

D. The method of A, in which L-isovalerylcarnitine is administered.

E. The method of A, in which L-propionylcarnitine is administered.

F. The method of A, wherein 0.01 mg–15 g per day of L-acetylcarnitine are administered.

G. The method of A, wherein 0.1 mg–10 g per day of L-acetylcarnitine are administered.

H. The method of A, wherein 0.01 mg–15 g per day of L-isovalerylcarnitine are administered.

I. The method of A, wherein 0.1 mg–10 g per day of L-isovalerylcarnitine are administered.

J. The method of A, wherein 0.01 mg–10 g per day of L-propionylcarnitine are administered.

K. The method of A, wherein 0.1 mg–10 g per day of L-propionylcarnitine are administered.

L. A pharmaceutical composition which may be administered orally, parenterally, nasally or topically for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1, selected from the group comprising neuropathies of the optic nerve and of the olfactory nerve, neuralgia of the trigeminal nerve, Bell's paralysis, amyotrophic lateral sclerosis and other motor neuron diseases, degeneration of the retina, osteoporosis, arthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs, clinical syndromes of reduced height, cachexia and acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensitivity syndromes, diabetes, obesity, asthenia, myasthenia and heart asthenia, immunodefidences and reperfusion injuries, and for the cicatrization of wounds, the healing of ulcers, the treatment of burns, tissue regeneration particularly that of cutaneous, intestinal and hepatic tissue, and the formation of dentine, the composition including, as active principle, an amount of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or of pharmacologically acceptable salts thereof which is effective for

increasing the levels of IGF-1, and at least one pharmacologically acceptable excipient.

M. A method for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1 selected from the group including neuropathies of the optic nerve and of the olfactory nerve, neuralgia of the trigeminal nerve, Bell's paralysis, amyotrophic lateral sclerosis, osteoporosis, anthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs clinical syndromes of reduced height, cachexia and acute or chronic hepatic necrosis, Turner's syndrome, sarcopenia, growth hormone insensitivity syndromes, obesity, asthenia, myasthenia and heart asthenia, immunodeficiences and reperfusion injuries, and for the cicatrization of wounds, the healing of ulcers, the treatment of burns, tissue regeneration, cutaneous, intestinal and hepatic tissue regeneration and the formation of dentine, that includes orally, parenterally, nasally or topically administering, to a patient in need thereof, a composition, that includes, as active ingredients at least one selected from the group including L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine and pharmacologically acceptable salts thereof and mixtures thereof; and at least one selected from the group including L-carnitine, coenzyme Q10, vitamin E and Se-L-methionine and pharmaceutically acceptable salts and derivatives thereof and mixtures thereof.

EXAMPLES

The examples which follow are for the purpose of illustrating the invention and should in no way be understood as implying a limitation in the scope thereof.

Example 1

13 individuals infected with HIV were enrolled. Blood was taken before and after treatment with L-acetylcarnitine orally at a dosage of 3 g/day for 8 weeks. The levels of IGF-1 were measured using a kit supplied by Amersham Itaha s.r.l., Milan, and the results were expressed as ng of IGF-1/100 μl of serum.

TABLE 1

Patient #	Before	After
1	0.03	4.16
2	0.03	5
3	0.03	0.06
4	0.02	5
5	0.02	0.05
6	0.04	3.25
7	0.25	5
8	0.02	0.03
9	0.1	5
10	0.07	5
11	0.03	5
12	0.16	3.49
13	0.03	0.18
AVERAGE	0.06	3.17
Standard deviation	0.07	2.22
Standard error	0.02	0.62
Student test		0.0002

It is known that individuals infected with HIV can have variable levels of IGF-1 in their serum. The experiments reported here demonstrated that the oral administration of L-acetylcarnitine increases the levels of IGF-1 in peripheral blood.

Example 2

Four Patients aged above 70 and with healthy dispositions were treated with 2 grams/day of L-acetylcarnitine parenterally for 7 days. The results of the doses of IGF-1 before and after the treatment are reported in Table 2.

TABLE 2

Patient #	Before	After
1	0.01	2.1
2	0.02	3.6
3	0.05	1.8
4	0.03	3.8
AVERAGE	0.03	2.83
Standard deviation	0.02	1.02
Standard error	0.008	0.51
Student test		0.01

Example 3

In this example, 60 subjects with chronic HCV infection were divided into three groups as follows:

A. to be treated with the formulation (2 sachets/day);

B. to be treated with the formulation plus α-IFN (18 millions/week); and

C. to be treated with α-IFN and the formulation at the above dosage; and were treated with a composition containing the following:

ACTIVE INGREDIENTS (POTENCY 100%):	
L-Carnitine base	mg 100
Acetyl-L-Carnitine HCl	mg 100
Coenzyme Q10	mg 20
Vitamin E	mg 10
Se-L-Methionine	mcg 50.

Derivatives of the described active ingredients (corrected to potency 100%) may be also be used.

Inactive Components

D-Mannitol

Sucrose

Saccharin Sodium

Providone

Flavouring Agents

Colouring Agents

Purified Water (not present in the final product)

Ethanol (not present in the final product).

The length of the treatment was one month followed by another 4 weeks of follow-up. All the patients were examined before treatment, after one month and after two months for clinical signs and symptoms related to their illness, side effects or toxicities. In addition the efficacy (or inefficacy) of the composition was monitored by measuring liver enzymes—as parameters of hepatic necrosis-, IGF-1 levels and mitochondrial functionality, at the different time points.

The present invention can lead to a new therapeutic strategy for HCV treatment as well as other conditions where IGF-1 levels are deficient and lead to increased and/or prolonged cell death (i.e. HIV-infection, retinal damage, etc . . . such as those listed above). This formulation can be given as dietary supplement or as a drug.

Other inactive components may be also used in addition to or in place of those listed above. Preferred examples thereof include acidifying agents (citric acid, fumaric acid, hydrochloric acid, malic acid etc.); alkalinizing agents (sodium bicarbonate, potassium citrate, sodium citrate, sodium carbonate etc.); cellulose (different types and grades); derivatives of cellulose (different types and grades); sorbitol; polyethylene glycols (different grades); colloidal

silicon dioxide; magnesium stearate; stearic acid; starch (different types and grades); emulsifying agents; preservatives; chelating agents; glidants; diluents; granulating agents; and solvents.

The entire contents of each of U.S. application Ser. No. 09/147,465, filed Jan. 4, 1999; international application PCT/IT97/00113, filed May 15, 1997; and Italian application RM 96 A 000479, filed Jul. 5, 1996 are hereby incorporated hy reference.

What is claimed is:

1. A mcthod for increasing thc lcvcl of IGF-1, comprising administering to a patient in need thereof a composition, comprising, as active ingredients:

at least one selected from the group consisting of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine and pharmacologically acceptahle salts thereof and mixtures thereof; and

at least one selected from the group consisting of L-carnitine, coenzyme Q10, vitamin E and Se-L-methionine and pharmaceutically acceptable salts and derivatives thereof and mixtures thereof.

2. The method of claim 1, wherein said composition comprises L-caroitine or a pharmacologically acceptable salt thereof.

3. The method of claim 2, wherein said pharmacologically acceptable salt is a chloride, bromide, iodide, aspartate, hydrogen aspartatc, citratc, hydrogen citratc, tartratc, phosphate, hydrogen phosphate, fumarate, hydrogen fumarate, glycerophosphate, glucose phosphate, lactate, maleate, hydrogen maleate, orotate, oxalate, hydrogen oxalate, sulfate, hydrogen sulfate, trichloroacetate, trifluoroacetate, or methanesulphonate.

4. The method of claim 1, wherein said composition comprises coenzyme Q10.

5. The method of claim 1, wherein said composition comprises vitamin E.

6. The method of claim 1, wherein said composition comprises Se-L-methionine or a pharmacologically acceptable salt thereof.

7. The method of claim 6, wherein said pharmacologically acccptablc salt is a chloridc, hromidc, iodidc, aspartatc, hydrogen aspartate, citrate, hydrogen citrate, tartrate, phosphate, hydrogen phosphate, fumarate, hydrogen fumarate, glycerophosphate, glucose phosphate, lactate, maleate, hydrogen maleate, orotate, oxalate, hydrogen oxalate, sulfate, hydrogen sulfate, trichloroacetate, trifluoroacetate, or methanesulphonate.

8. The method of claim 1, wherein said composition comprises L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine and/or pharmacologically acceptable salts thereof.

9. The method of claim 8, wherein said pharmacologically acceptable salt is a chloride, hromide, iodide, aspartate, hydrogen aspartate, citrate, hydrogen citrate, tartrate, phosphatc, hydrogcn phosphatc, fumaratc, hydrogen fumarate, glycerophosphate, glucose phosphate, lactate, maleate, hydrogen maleate, orotate, oxalate, hydrogen oxalate, sulfate, hydrogen sulfate, trichloroacetate, trifluoroacetate, or methanesulphonate.

10. Thc mcthod of claim 1, whcrcin said composition comprises L-acetylcarnitine or a pharmacologically acceptahle salt thereof.

11. The method of claim 10, wherein said pharmacologically acceptable salt is a chloride, bromide, iodide, aspartate, hydrogen aspartate, citrate, hydrogen citrate, tartrate, phosphate, hydrogen phosphate, fumarate, hydrogen fumarate, glycerophosphate, glucosc phosphate, lactate, malcatc, hydrogcn malcatc, orotatc, oxalatc, hydrogcn oxalate, sulfate, hydrogen sulfate, trichloroacetate, trifluoroacetate, or methanesulphonate.

12. The method of claim 1, wherein said composition comprises L-isovalerylcarnitine or a pharmacologically acceptable salt thereof.

13. The method of claim 12, wherein said pharmacologically acceptable salt is a chloride, bromide, iodide, aspartate, hydrogen aspartate, citrate, hydrogen citrate, tartrate, phosphate, hydrogen phosphate, fumarate, hydrogen fumarate, glycerophosphate, glucose phosphate, lactate, maleate, hydrogeo maleate, orotate, oxalate, hydrogen oxalate, sulfate, hydrogen sulfate, trichloroacetate, trifluoroacetatc, or methanesulphonatc.

14. Thc mcthod of claim 1, whcrcin said composition comprises L-propionylcarnitine or a pharmacologically acceptable salt thereof.

15. The method of claim 14, wherein said pharmacologically acceptable salt is a chloride, bromide, iodide, aspartate, hydrogen aspartate, citrate, hydrogen citrate, tartrate, phosphate, hydrogen phosphate, fumarate, hydrogen fumarate, glycerophosphate, glucose phosphate, lactate, maleate, hydrogen maleate, orotate, oxalate, hydrogen oxalate, sulfate, hydrogen sulfate, trichloroacetate, trifluoroacetate, or methaoesulphooate.

16. The method of claim 1, wherein said compositioo further comprises a pharmaceutically acceptable excipient.

17. The method of claim 1, wherein said composition is administered orally, parcnterally, nasally, or topically.

18. The method of claim 1, wherein 0.01 mg to 15 g per day of active ingredients are administered.

19. The method of claim 1, wherein 0.1 mg to 10 g per day of active ingredients are administered.

20. The method of claim 1, wherein said pharmacologically acceptable salt is a chloride, bromide, iodide, aspartate, hydrogen aspartate, citrate, hydrogen citrate, tartrate, phosphate, hydrogen phosphate, fumarate, hydrogen fumarate, glycerophosphate, glucose phosphate, lactate, maleate, hydrogeo maleate, orotate, oxalate, hydrogen oxalate, sulfate, hydrogen sulfate, trichloroacetate, trifluoroacetate, or methanesulphonate.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,380,252 B1
DATED : April 30, 2002
INVENTOR(S) : De Simone

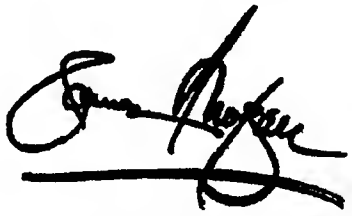
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [30], **Foreign Application Priority Data**, information should read:

-- [30] **Foreign Application Priority Data**
Jul. 5, 1996 (IT) RM96A0479

Signed and Sealed this

Fourteenth Day of January, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT D

US006063820A

United States Patent [19]

Cavazza

[11] Patent Number: 6,063,820

[45] Date of Patent: May 16, 2000

[54] **MEDICAL FOOD FOR DIABETICS**

[75] Inventor: **Claudio Cavazza**, Rome, Italy

[73] Assignee: **Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.**, Rome, Italy

[21] Appl. No.: **09/040,341**

[22] Filed: **Mar. 18, 1998**

[30] **Foreign Application Priority Data**

Mar. 20, 1997 [IT] Italy RM97A0155

[51] **Int. Cl.**[7] **A01N 31/00**; A01N 37/30; A01N 37/02; A01N 37/12

[52] **U.S. Cl.** **514/739**; 514/556; 514/547; 514/551; 514/866

[58] **Field of Search** 514/556, 547, 514/551, 739, 866

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,037,851	8/1991	Cavazza	514/556
5,043,355	8/1991	Cavazza	514/547
5,145,871	9/1992	Cavazza	514/546
5,173,508	12/1992	Cavazza	514/547
5,192,805	3/1993	Cavazza	514/556
5,227,518	7/1993	Cavazza	560/253
5,270,472	12/1993	Taglialatela et al.	560/251
5,418,253	5/1995	Cavazza et al.	514/547
5,430,065	7/1995	Cavazza	514/556
5,432,199	7/1995	Cavazza	514/546
5,494,924	2/1996	Cavazza et al.	514/357
5,534,549	7/1996	Tinti et al.	514/556
5,591,450	1/1997	Cavazza et al.	514/547
5,614,556	3/1997	Cavazza et al.	514/546
5,627,212	5/1997	Cavazza et al.	514/547
5,637,305	6/1997	Cavazza et al.	514/547
5,639,767	6/1997	Cavazza et al.	514/547
5,747,536	5/1998	Cavazza	514/556
5,753,703	5/1998	Cavazza et al.	514/547

OTHER PUBLICATIONS

McCarty et al. Medical Hypotheses, 13(2) 139–51 (Abstract), 1984.

Primary Examiner—Theodore J. Criares

Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

[57] **ABSTRACT**

A medical food for diabetics is disclosed which comprises as characterizing active ingredients γ-linolenic acid and at least one alkanoyl-L-carnitine, e.g. acetyl-L-carnitine and/or propionyl-L-carnitine.

15 Claims, No Drawings

MEDICAL FOOD FOR DIABETICS

MEDICAL FOOD FOR DIABETICS

The present invention relates to a therapeutic/nutritional composition (medical food) for diabetics.

Diabetes mellitus is a complex syndrome of differing genetic, environmental and pathogenetic origin.

This syndrome in any event is characterised by hyperglycaemia due to impaired insulin secretion and/or efficiency, associated with a risk of diabetic ketoacidosis or non-ketotic hyper-glycaemic-hyperosmolar coma. Among the late complications of the disease, those worthy of particular mention are nephropathy, retinopathy, atherosclerotic coronary disease, peripheral arteriopathies and neuropathies of the autonomic nervous system.

Traditionally, a distinction is made between insulin-dependent diabetes mellitus (type 1 DM) and non-insulin-dependent diabetes (type 2 DM).

Type 1 DM, which commonly develops in infancy or during adolescence, is characterised clinically by hyperglycaemia and a predisposition to diabetic ketoacidosis. Chronic insulin treatment is necessary to control the disease.

Type 2 DM is characterised clinically by hyperglycaemia not associated with a predisposition to diabetic ketoacidosis. In type 2 DM, the hyperglycaemia stems both from an abnormal insulin secretory response to glucose and from "insulin-resistance", i.e. from a reduced activity of insulin itself.

Although the therapies of choice in the therapeutic treatment of type 1 and type 2 DM, based essentially on the administration of insulin and of oral hypoglycaemic agents, yield substantial efficacy, appropriate nutritional therapy is also of major importance for the successful treatment of diabetics.

There are three key rules when tackling diabetes from the therapeutic/nutritional standpoint. First of all, diabetics need to maintain blood glucose levels as close as possible to normal values, striking the right balance between physical activity and food intake, on the one hand, and the administration of insulin and hypoglycaemic agents, on the other. Diabetics should therefore increase their intake of nutrients capable of enhancing the body's ability to metabolise glucose and insulin. Lastly, they should increase their intake of nutrients which reduce the risk of diabetic complications.

A number of micronutrients perform both the second and third functions.

Broadly speaking, the alimentary requirements of vitamins and mineral salts in diabetics under adequate metabolic control are similar to those of a normal person and should therefore comply with the amounts recommended by the Food and Nutrition Board. However, micronutrient deficiencies have been found in patients maintained on diets with a high fibre content or in those suffering from acidosis or glycosuria. Moreover, experimental evidence has suggested that vitamins, mineral salts and other micronutrients are capable of contributing towards protecting diabetic patients from complications such as heart disease, peripheral neuropathy, retinopathy, kidney failure, frequent infections and slow wound healing.

To date, particular attention has been focused upon the development of medical foods for diabetics which contribute, along with suitable pharmacological treatment, towards lowering plasma glucose levels. For example, EP 0 659 349 A1 (Bristol-Myers.Squibb Co.) describes a medical food of this type in which the characterising ingredient is myo-inositol, the hypoglycaemic activity of which was, moreover, already well known.

One further characteristic of diabetes is abnormal metabolism of essential fatty acids.

Essential fatty acids such as linoleic acid and alphalinolenic acid (parent acids of the omega-6 and omega-3 essential fatty acid series, respectively) are nutritional substances which, like vitamins, have to be supplied via the diet, in that they are not biosynthesised by the body.

It has been demonstrated that the activity of omega-6-desaturase, the enzyme controlling the conversion kinetics of linoleic acid in the precursors of prostaglandins is reduced in diabetes, as are the tissue levels of essential fatty acids. The production of vascular prostacyclin also appears to be diminished.

An object of the present invention is to provide a medical food for diabetics which enables them to compensate for the reduced metabolism of essential fatty acids typical of such subjects. In particular, the object of the present invention is to provide a medical food of this type which makes it possible to by-pass the enzyme blockade caused by the reduced activity of omega-6-desaturase which occurs in diabetics and gives rise to inadequate conversion of linoleic acid into γ-linolenic acid and thus to a reduced production of prostaglandin and leukotriene precursors.

The therapeutic/nutritional composition for diabetics of the present invention comprises a mixture of:

(a) γ-linolenic acid or a pharmacologically acceptable salt thereof; and

(b) at least one alkanoyl-L-carnitine wherein the alkanoyl group is a straight or branched alkanoyl having 2–6 carbon atoms, or a pharmacologically acceptable salt thereof;

wherein the amounts of (a) and (b) are effective to exert a synergistic effect in compensating for the defects of the essential fatty acid metabolism and preventing diabetic complications, particularly diabetic neuropathy, and bringing about regression thereof.

Preferably, the alkanoyl-L-carnitine is selected from the group comprising acetyl-, propionyl-, butyryl-, valeryl-, and isovaleryl-L-carnitine or a pharmacologically acceptable salt thereof; acetyl-L-carnitine and propionyl-L-carnitine are particularly preferred.

What is meant by pharmacologically acceptable salts of an alkanoyl-L-carnitine are any of its salts with an acid that does not give rise to unwanted side effects. Such acids are well known to pharmacologists and to experts in pharmacy and pharmaceutical technology.

A list of FDA-approved pharmacologically acceptable acids is disclosed in Int. J. of Pharm. 33, (1986), 201–217, which is incorporated herein by reference.

The composition of the present invention may further comprise vitamins, metals, coenzymes, organic or inorganic antioxidants or precursors thereof.

Preferably, the coenzyme is coenzyme Q10, the organic antioxidant is selected from the group comprising lipoic acid, resveratrol and glutathione and a preferred precursor is N-acetyl-L-cysteine. Selenium is a preferred example of inorganic antioxidant.

A first preferred embodiment of composition according to the invention comprises in admixture the following components:

γ-linolenic acid or a pharmacologically acceptable salt thereof; acetyl-L-carnitine or a pharmacologically acceptable salt thereof;

Taurine;
Pantethine;
Vitamin A;
Vitamin E;
Vitamin B_1;
Vitamin B_6;
Vitamin B_{12};
Magnesium;
Calcium;
Zinc;
Selenium;
Chromium; and
Vanadium.

A second preferred embodiment of composition further comprises coenzyme Q10, lipoic acid and myo-inositol.

A third preferred embodiment of composition comprises all the components of the first or second composition, a mixture of acetyl- and propionyl-L-carnitine (molar ratio from 10:1 to 1:10) substituting for acetyl-L-carnitine alone.

In order to be nutritionally complete, the composition of the invention can advantageously comprise also a fat source, a protein source and a carbohydrate source sufficient to meet the caloric daily need of a diabetic individual.

Preferably, this nutritionally complete composition comprises form 10 to 15% of proteins, from 35 to 45% of lipids and from 40 to 50% of carbohydrates the percentages being calculated on the overall caloric intake of the composition.

At any rate, it was found advantageous that anyone of the compositions of the present invention, suitable both for a monodose administration regimen and a multidose administration regimen, be apt to supply 350–500 mg/day of γ-linolenic acid and 1.5–2.5 mg/day of acetyl-L-carnitine.

It is unexpected and surprising that γ-linolenic acid and the alkanoyl-L-carnitine (i.e. the characterizing components of the present composition) act synergistically in enhancing the compensation of defects in essential fatty acids metabolism, or the prevention or reversal of diabetic complications, particularly diabetic neuropathy.

The further composition components are valuable for the following reasons:

Taurine, one of the most abundant amino acids in the body, is found in the central nervous system, skeletal muscles and is very concentrated in the brain and heart. Taurine deficiency is associated with retinal degeneration.

Diabetic patients have below-normal levels of taurine in blood and platelets.

Taurine administration to insulin-dependent patients was demonstrated to reduce platelet aggregation and prevent retinopathy by preventing blood clots in retinal vessels.

Pantethine is a constituent of coenzyme A, which facilitates energy production through enhancement of the metabolic pathways of fatty acid β-oxidation and the formation of acetyl-CoA.

Recent clinical trials have shown that pantethine administration to hyperlipidemic diabetic subjects was able to decrease serum total cholesterol and to increase HDL-cholesterol. Furthermore, pantethine normalized platelet volume, microviscosity and lipid composition and concomitantly reduced platelet aggregation.

Vitamin A, whose Recommended Dietary Allowance (RDA) is 1000 μg/day for adult males and 800 μg/day for adult females, has a diphasic concentration-dependent effect on insulin release. At low concentrations, vitamin A stimulates insulin release while at high concentrations it has an inhibitory effect which may be mediated in part by impairement of intracellular glucose oxidation.

Vitamin A administration to type II diabetic patients reduces insulin resistance and hastens the healing process by stimulating collagen synthesis.

The reversal of early signs of diabetic retinopathy, and apparent cessation or deceleration of the progression of more advanced proliferative retinopathy was demonstrated in diabetic patients receiving vitamin A.

The need for vitamin E whose RDA is 10 mg/day for males and 8 mg/day for females increases with higher intakes of polyunsaturated fatty acids.

Vitamin E is the most active antioxidant agent present in biological membranes where it protects cellular structures against damage from oxygen free radicals and reactive products of lipid peroxidation, thus contributing to membrane stability.

Platelet activity and eicosanoid production can be normalized by vitamin E supplementation in diabetic patients.

Vitamin B1, whose RDA is 0.5 mg/100 K calories (a minimal intake of 1 mg/day is recommended) plays a key role in energy metabolism.

The daily requirement of vitamin B1 is dependent on the intake of carbohydrates.

Vitamin B6 RDA is about 2 mg/day in normal adults.

Vitamin B6 occurs in 3 forms: pyridoxine hydrochloride, pyridoxal and pyridoxamine and is a component of approximately 120 enzymes.

In the form of pyridoxal phosphate it is a cofactor in the metabolism of amino acids and neurotransmitters and in the breakdown of glycogen; it can bind to steroid hormone receptors and can have a role in the regulation of their action.

Pyridoxine is involved in hemoglobulin formation.

Plasma vitamin B6 is often low in diabetic patients; those with poor control of blood glucose have more pronounced deficiency.

Pyridoxine deficiency in humans has been associated with glucose intolerance. The role of vitamin B6 in glucose homeostasis has been suggested by its effect on tryptophan metabolism.

Pharmacological doses of viamin B6 can reverse the abnormalities of tryptophan metabolism and may improve carbohydrate tolerance.

Vitamin B12 (RDA 2 μg/day, usual intake 4–8 μg/day) plays a pivotal role in amino acid metabolism. The B12 coenzyme catalyzes amino and fatty acid breakdown.

Vitamin B12 deficiency is associated particularly with insulin-dependent diabetes mellitus. Pernicious anemia and diabetes inellitus can occur in the same individual as part of a polyglandular autoimmune syndrome.

Magnesium (RDA 350 mg/day for adult males and 280 mg/day for females) plays an essential role in many enzymatic reactions such as the transfer of phosphate groups, the acylation of CoA and the hydrolysis of phosphate and pyrophosphate; it is important for the activation of amino acids, the aggregation of ribosomes and the synthesis and degradation of DNA.

Magnesium is involved in glucose homeostasis at multiple levels: it is a cofactor in the glucose transport system of plasma membranes; has an important role in activity of various enzymes involved in glucose oxidation, may play a role in release of insulin, and can modulate the mechanisms of energy transfer from high-energy phosphate bonds.

Diabetes mellitus is associated with increased urinary loss of magnesium especially when hyperglycemia is poorly controlled. Plasma magnesium concentration in diabetic patients is reduced. Of particular concern is the large urinary magnesium loss during diabetic ketoacidosis that causes hypomagnesemia and can induce life threatening effects on myocardium, skeletal muscles and is implicated in insulin resistance.

Magnesium deficiency has been linked to two common complications of diabetes, namely retinopathy and ischemic heart disease.

Calcium (RDA about 1 g/day for adult women and men) is the most common mineral in the human body where it has structural, electrophysiological and regulatory functions.

Diabetic patients are at increased risk for osteoporosis, presumably due to increased urinary calcium loss.

Dietary calcium competitively inhibits magnesium absorption, thus it should only be administered in conjunction with supplementary magnesium.

Zinc (RDA 15 mg/day for males and 12 mg/day for females) plays structural, enzymatic and regulatory roles. It participates to the activity of over 60 enzymes such as carboxypeptidase, carbonic anhydrase and alcohol dehydrogenase. It has a role in neuronal activity and memory and is necessary for the maintenance of normal plasma levels of Vitamin A.

Diabetes mellitus may lead to zinc deficiency. Low blood zinc and hyperzincuria have been reported in initial stages of both Type I and Type II diabetes mellitus.

Zinc is well established as playing a role in wound healing and maintenance of skin integrity because of its promoting activity in protein synthesis, cellular replication and collagen formation.

High concentrations or doses of zinc have antioxidant-like effects both in vitro and in vivo.

Selenium (RDA 70 μg/day for adult males and 55 μg/day for adult females) is an integral part of glutathione peroxidase and consequently plays a protective role against tissue damage caused by peroxides produced from lipid metabolism.

Selenium deficiency in humans causes decreased glutathione peroxidase activity and cardiomyopathy. Moreover, increased intakes of selenium may reduce the risk of cardiovascular diseases, reverses early signs of diabetic retinopathy, and brings about apparent cessation or deceleration of the progression of more advanced proliferative retinopathy.

Chromium's Estimated Safe and Adiquate Daily Dietary Intake (ESADDI) for adults of both sexes is from 50 to 200 mg/day.

Chromium is an essential nutrient required for normal carbohydrate and lipid metabolism. It is a component of the biological active glucose-tolerance factor whose deficiency is implicated in the pathogenesis of some forms of glucose intolerance and diabetes mellitus.

Urinary chromium excretion tends to increase in diabetics.

Vanadium's ESADDI is about 100 μg/day; bioavailability is very low, generally less than 1%.

Vanadium has an insulin-like behavior in insulin-dependent diabetics. It either mimics the effects of insulin or increases its efficiency, reducing both glucose and insulin levels.

The administration of vanadium to type II diabetic patients improves glucose tolerance, lowers blood glucose levels and decreases blood cholesterol levels.

I claim:

1. A therapeutic/nutritional composition, comprising a mixture of:

(a) γ-linolenic acid or a pharmacologically acceptable salt thereof; and

(b) at least one alkanoyl-L-carnitine in which the alkanoyl group is a straight or branched alkanoyl group having 2–6 carbon atoms, or a pharmacologically acceptable salt thereof, which components act synergistically to enhance the compensation for defects in essential fatty acid metabolism of a diabetic or preventing or reversing diabetic neuropathy.

2. The composition of claim 1, wherein the alkanoyl-L-carnitine is selected from the group comprising acetyl-, propionyl-, butyryl-, valeryl-, and isovaleryl-L-carnitine or a pharmacologically acceptable salt thereof.

3. The composition of claim 1, which comprises acetyl-L-carnitine and propionyl-L-carnitine or the pharmacologically acceptable salts thereof, wherein their molar ratio is 10:1 to 1:10.

4. The composition of claim 1, further comprising vitamins and metals.

5. The composition of claim 4 which comprises a mixture of the following components:

γ-linolenic acid or a pharmacologically acceptable salt thereof;

acetyl-L-carnitine or a pharmacologically acceptable salt thereof;

the linolenic acid and acetyl-L-carnitine being present in synergistic effective amounts;

Taurine;

Pantethine;

Vitamin A;

Vitamin E;

Vitamin B_1;

Vitamin B_6;

Vitamin B_{12};

Magnesium;

Calcium;

Zinc;

Selenium;

Chromium; and

Vanadium.

6. The composition of claim 5, which comprises acetyl-L-carnitine and propionyl-L-carnitine or the pharmacologically acceptable salts thereof wherein their molar ratio is 10:1 to 1:10.

7. The composition of claim 1, which further comprises a coenzyme and/or an inorganic or organic antioxidant or a precursor thereof.

8. The composition of claim 7, wherein the coenzyme is coenzyme Q10, the organic antioxidant is selected from the group comprising lipoic acid, resveratrol or glutathione and the precursor is N-acetyl-L-cysteine.

9. The composition of claim 5, which further comprises coenzyme Q10, lipoic acid and myo-inositol.

10. The composition of claim 1 as a nutritionally complete composition further comprising a lipid component, a protein component and a carbohydrate component, suitable to provide the caloric daily intake needed by a diabetic individual.

11. The composition of claim 10 which comprises from 10 to 15% of proteins, from 35 to 45% of lipids and from 40 to 50% of carbohydrates, the percentages being calculated on the overall caloric intake of the composition.

12. The composition of claim 1 suitable to supply, in a single or multiple dose administration regimen, from about 350 to 500 mg/day of γ-linolenic acid and from 1.5 to 2.5 g/day of acetyl-L-carnitine.

13. A method for compensating for defects of essential fatty acid metabolism in diabetics, comprising:

administering synergistic effective amounts of a therapeutic/nutritional composition comprising a mixture of:

(a) γ-linolenic acid or a pharmacologically acceptable salt thereof; and

(b) at least one alkanoyl-L-carnitine, wherein the alkanoyl group is a C_{2-6} straight or branched alkanoyl group or a pharmacologically acceptable salt thereof, to a subject suffering from diabetes.

14. A method of preventing diabetic complications, comprising:

administering synergistic effective amounts of a therapeutic/nutritional composition comprising a mixture of:

(a) γ-linolenic acid or a pharmacologically acceptable salt thereof; and

(b) at least one alkanoyl-L-carnitine, wherein the alkanoyl group is a C_{2-6} straight or branched alkanoyl group or a pharmacologically acceptable salt thereof, to a subject suffering from diabetes.

15. The method of claim **14**, wherein said diabetic complication is diabetic neuropathy.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

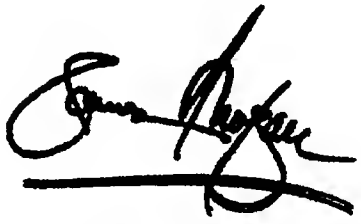
PATENT NO. : 6,063,820
DATED : May 16, 2000
INVENTOR(S) : Claudio Cavazza

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 3,
Line 33, "1.5-2.5 mg/day" should read -- 1.5-2.5 g/day --

Signed and Sealed this

Ninth Day of April, 2002



Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT E

US006348495B1

(12) **United States Patent**
Cavazza et al.

(10) **Patent No.: US 6,348,495 B1**
(45) **Date of Patent: Feb. 19, 2002**

(54) **METHOD FOR TREATING CELIAC DISEASE**

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Related U.S. Application Data

(60) Continuation-in-part of application No. 09/441,328, filed on Nov. 16, 1999, now Pat. No. 6,143,785, which is a division of application No. 08/868,627, filed on Jun. 4, 1997, now Pat. No. 6,013,607.

(30) **Foreign Application Priority Data**

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(58) **Field of Search** 514/642, 547, 514/556

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,958,418 A 9/1990 Dufour 24/713.6

FOREIGN PATENT DOCUMENTS

JP	1-156927	6/1989
WO	WO 97/272177	7/1997
WO	WO 99/56698	11/1999

OTHER PUBLICATIONS

Lerner et al, Gut (1993) 34,933–935 Serum carnitine concentrations in coeliac disease.
Ceccarelli et al Minerva Pediatrica (1992) vol. 44, No. 9, 401–405 Concentrazioni plasmatiche di L–carnitine in bambini celiaci.
English translation Italian patent appln. RM 96A 00396 filed Jun. 6, 1996.

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(57) **ABSTRACT**

A method for treating celiac disease comprising administration of a composition containing an alkanoyl L-carnitine wherein the alkanoyl group is straight or branched and has 2–6 carbon atoms and the pharmacologically acceptable salts thereof.

20 Claims, No Drawings

METHOD FOR TREATING CELIAC DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of earlier application Ser. No. 09/441,328 filed Nov. 16, 1999, now U.S. Pat. No. 6,143,785, which is a division of Ser. No. 08/868,627 filed Jun. 4, 1997, now U.S. Pat. No. 6,013,607.

The present invention relates to a new therapeutic use of the lower alkanoyl L-carnitines and their pharmacologically acceptable salts to produce pharmaceutical compositioos for the treatment of chronic intestioal disorders, io particular inflammatory bowel diseases, more particularly, ulcerative colitis or celiac disease.

The present invention also relates to pharmaceutical compositions suitable for rectal administration, particularly in the form of foams or enemas, containing the above-mentioned alkanoyl L-carnitines.

Ulcerative colitis is an inflammatory, ulcerative disease of the colon of unknown aetiology, very often characterised by haematic diarrhoea.

It usually originates in the recto-sigmoid area, from which it may spread proximally with possible involvement of the entire colon. Alternatively, it may attack a substantial portion of the large bowel right from the outset.

The complications of ulcerative colitis are particularly severe: it has been documented, in fact, that there is an enormous increase in the risk of colon cancer in patients suffering from ulcerative colitis. The incidence of colon cancer increases with both involvement of the entire colon and with a duration of disease exceeding 10 years.

In both the mild-to-moderate forms and the moderately or distinctly severe forms of the disease, corticosteroids constitute the drugs of choice, namely hydrocortisone, betamethasone and prednisone.

In the mild-to-moderate forms, physiological solution containing hydrocortisone is administered via an enema which is retained in the bowel as long as possible.

In the moderately severe forms, systemic corticosteroid therapy is necessary, consisting generally in 10–15 mg of prednisone t.i.d. or q.i.d. per os, which is capable of inducing drastic remission.

In the more severe forms requiring admission to hospital, the corticosteroid therapy is administered parenterally.

Both the systemic and topical administration of these drugs gives rise to serious side effects, mainly related to interference with the hypothalamo-pituitary-adrenal axis.

The side effects due to topical treatment of ulcerative colitis with these traditional corticosteroids are, far instance, transient or prolonged depression of adrenocortical function, weight gain, acne and moon face.

Though it is well known, particularly in the moderately severe forms of the disease, that the daily corticosteroid dose can be gradually reduced to 10–20 mg per week after 1–2 weeks of treatment, even such low corticosteroid doses continue to induce harmful side effects, the elimination or at least the drastic reduction of which constitutes a therapeutic goal of primary importance.

Celiac disease (or celiac syndrome) is a chronic intestinal disorder caused by a specific intolerance to gluten present in wheat, rye, barley and oats proteios included io the diet leading to dramatic changes in the small intestinal mucosa and subsequent impaired absorption. The celiac syndrome

can affect genetically susceptible subjects (around 3‰). Symptoms comprise diarrhoea and other malabsorption symptoms, including total atrophy of intestinal mucosa.

It is known that in humans said pathologic alterations are produced by the action on the intestinal mucosa of digestion products of wheat gluten and, in particular, by the 70% ethanol soluble gluten protein fraction. Said protein fraction, generally name as "prolamin" (in wheat, in particular, it is named as "gliadin"), is present in several cereals in different proportions and is composed of numerous proteins with different molecular weights, and having an high glutamine (one glutamine residue every three amino acids) and proline (a proline residue every seven amino acids) content, and a low ionic streogth (due to few residues able to ionise in solution).

Current treatment is effected by a well balanced gluten-gliadin-free diet high in calories and proteins and normal in fat. This excludes cereal grains with the exception of rice and corn. Patients affected by celiac disease not responding to gluten-gliadin-free diet are treated with glucocorticoid steroids. For example U.S. Pat. No. 4,958,418, assigned to Glaxo Group Limited, teaches the use of fluticasone dipropionate, an anti-inflammatory steroid, This patent clearly establishes that celiac disease, ulcerative colitis and Crohn's disease are all embedded in the category of bowel diseases which respond to treatment of glucocorticoid steroids.

Based on the study of toxic peptides obtained by different prolamins, WO 97/27217, in the name of Istituto Superiore di Sanita, provides a protein compound having a sequence comprised in the proteins of durum wheat and being not toxic for celiac subjects, in particular a protein of the following sequence: QQPQDAVQPF.

WO 99/56698, in the name of Copenhagen University, discloses a method for treating celiac disease comprising interfering with the deamidation of at least one glutamine residue in a gliadin molecule. Practically, the treatment comprises administering to a patient suffering from celiac syndrome at least one of the following substances: a) a substance capable of increasing the pH in the gastroduodenal tract, e.g. an antacid, an anticholinergic agent, H2-receptor antagonists or a proton pump inhibitor, b) an antibiotic or antimicrobial agent acting against deamidating bacteria and/or a substance capable of interfering with deamidating enzymes. In a wide sense, a method for treating celiac disease is prospected in JP 1156927, to University Leland Stanford, by administering an antagonist to IFN-$_{65}$.

There is still a strong need to make available a method for the treatment of celiac disease using a simple therapeutic scheme, with an easily managed drugs, with low or null side effects. The cost of the drug is also important.

Celiac patients, children in particular, proved to have low serum L-carnitine levels, most likely due to the damaged bowel mucosa (Lerner A. et al., Gut; 34: 933–935; Ceccarelli M. et al. Minerva Pediatr. 1992; 44:401–5). Indeed, celiac patients do, not absorb hexogenous L-carnitine. From a clinical point of view, L-carnitine deficiency cannot be associated to celiac disease. To date, it has never been demonstrated that L-carnitine deficiency may give celiac disease.

Therefore, it was totally unexpected to find that an alkanoyl L-carnitine is effective in the treatment of celiac disease according to is the teaching of the present inveotion. The object of the present invention is to provide a method for treating and pharmaceutical compositions useful for the treatment of chronic intestinal disorders, in particular

EXHIBIT G

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(54) **NUTRITIONAL SUPPLEMENTS FOR MATURE PETS**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 09/770,535, filed on Jan. 25, 2001, now abandoned.

(60) Provisional application No. 60/178,073, filed on Jan. 25, 2000. Provisional application No. 60/223,586, filed on Aug. 7, 2000.

Publication Classification

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(52) **U.S. Cl.** **514/440**; 424/94.1; 514/561; 514/546

(57) **ABSTRACT**

Disclosed herein are compositions to meet the needs of aged pets and other animals. A pet food formulated for senior pets provides α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day. A pet treat for senior pets provides α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day. A pet supplement for mature pets offers α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

NUTRITIONAL SUPPLEMENTS FOR MATURE PETS

CROSS RELATED

[0001] This application is a continuation in part of U.S. application Ser. No. 09/770,535, filed Jan. 25, 2001, which claims the benefit of U.S. Provisional Application No. 60/178,073, filed Jan. 25, 2000, and U.S. Provisional Application No. 60/223,586, filed Aug. 7, 2000.

TECHNICAL FIELD

[0002] The present invention is generally directed to pet food and dietary supplements. More specifically, the present invention relates to the addition of the combination of lipoic acid and carnitine to these compositions. Optional additional ingredients are coenzyme Q and creatine.

BACKGROUND OF INVENTION

[0003] Many pet foods contain nutrition for a specific stage of the pet's life. Stages of a pet's life are broken down as follows: kitten or puppy is up to 1 year, adult cat or dog is one to six years, and a senior cat or dog is over six years old. However, different animals age at different rates. Cats are often considered older or senior at seven to eight years of age and geriatric or very old at 10 to 12 years. Dogs often are considered older between 7.5 and 13.5 years of age. Dogs often are considered older when they reach half of their life expectancy, which corresponds to about five years for larger dogs and seven years for smaller dogs.

[0004] Today, pets are living markedly longer because of improved treatments for infections and parasites, improved diagnostics, and better medical technology. Improved nutrition also has played a role, particularly the life-stage concept that recognizes different nutritional needs at different ages.

[0005] Nutrition is particularly important in aging pets and in managing the risk factors of cancer, heart/cardiac, kidney and liver disease which are prominent causes of non-accidental death in dogs and cats. In addition, older pets become less active and have reduced lean body mass. For these two reasons, pets require less energy from their food. Aging pets also have a reduced immune response and glucose tolerance.

[0006] The goals of pet foods for older animals have been stated as maintaining optimal nutrition, managing risk factors, managing diseases, and improving quality and longevity of life. So far, that has meant reducing protein, fat, energy sources, phosphorus and sodium and increasing water and fiber. However, very old dogs (greater than 12 years) may require somewhat more fat and energy sources.

[0007] An example of a formulation for older dogs is the Science Diet® Canine Senior® product that provides fewer calories, more fiber and lower phosphorus. The dry formula has 350 kcal/cup. It has the following nutrient contents per 100 kcal: protein 4.8 g, fat 2.8 g, carbohydrate 16.5 g, crude fiber 0.8 g, calcium 155 mg, phosphorus 144 mg, sodium 45 mg, potassium 163 mg, chloride 141 mg and magnesium 30 mg. It also contains the following vitamins: choline chloride, vitamin A, vitamin D3, vitamin E, niacin, thiamine, calcium pantothenate, pyridoxine hydrochloride, riboflavin, folic acid, biotin and vitamin B 12.

[0008] A canned turkey Canine Senior® formula provides about 393 kcal per 418-gram can. It has the following nutrient contents per 100 kcal: protein 4.9 g, fat 3.2 g, carbohydrate 15.8 g, crude fiber 0.5 g, calcium 159 mg, phosphorus 138 mg, sodium 43 mg, potassium 181 mg, chloride 149 mg and magnesium 23 mg. It also contains the following vitamins: D-activated animal sterol, vitamin E, niacin, thiamine, calcium pantothenate, pyridoxine hydrochloride, riboflavin, folic acid, biotin and vitamin B12.

[0009] The Science Diet Feline Senior™ canned fish formula offers lower energy and higher fiber than pet food for younger cats. It provides 150 kcal per 156-gram can. It has the following nutrient contents per 100 kcal: protein 9.5 g, fat 5.8 g, carbohydrate 5.3 g, crude fiber 1.1 g, calcium 219 mg, phosphorus 177 mg, sodium 115 mg, potassium 198 mg, chloride 177 mg, magnesium 17 mg, and taurine 146 mg. It also contains the following vitamins: vitamin A, D-activated animal sterol, vitamin E, niacin, thiamine, calcium pantothenate, pyridoxine hydrochloride, riboflavin, folic acid, biotin and vitamin B12.

[0010] Recent research has suggested that taking sufficient quantities of certain substances rejuvenates aged mitochondria, the failing powerhouses of cell metabolism. Numerous lines of evidence suggest that the organelles of cellular respiration, the mitochondria, degenerate with cellular aging (Shigenaga et al. PNAS 91: 10771, 1994). Unfortunately, the study of mitochondrial aging has been hampered because mitochondria isolated from older cells and host animals are fragile and heterogeneous. Hence the interpretation of any results is suspect as about half the mitochondria lyse during isolation. Recently a new method was developed for studying mitochondria in hepatocytes from old animals that avoids this problem (Hagen et al. PNAS 94, 3064-3069, 1997). Mitochondria from older animals are not only more fragile, but have about half the level of cardiolipin, a key lipid unique to mitochondria, without which they can not maintain a high membrane potential. Furthermore, Hagen et al. showed that in hepatocytes from older animals, the mitochondria are lower in membrane potential and leak more toxic oxidants.

[0011] Carnitine and carnitine derivatives have been used as metabolites in animal husbandry and for human diet and therapy. U.S. Pat. No. 5,362,753 (Method of increasing the hatchability of eggs by feeding hens carnitine); U.S. Pat. No. 4,687,782 (Nutritional composition for enhancing skeletal muscle adaptation to exercise training); U.S. Pat. No. 5,030, 458 (Method for preventing diet-induced carnitine deficiency in domesticated dogs and cats); U.S. Pat. No. 5,030, 657 (L-carnitine supplemented catfish diet); U.S. Pat. No. 4,343,816 (Pharmaceutical composition comprising an acyl-carnitine, for treating peripheral vascular diseases); U.S. Pat. No. 5,560,928 (Nutritional and/or dietary composition and method of using the same); U.S. Pat. No. 5,504,072 (Enteral nutritional composition having balanced amino acid profile); U.S. Pat. No. 5,391,550 (Compositions of matter and methods for increasing intracellular ATP levels and physical performance levels and for increasing the rate of wound repair); U.S. Pat. No. 5,240,961 (Method of treating reduced insulin-like growth factor and bone loss associated with aging); etc.

[0012] Similarly, mitochondrially active antioxidants including vitamins (especially C, E, B and D), glutathione,

N-acetyl cysteine, lipoic acid, etc., have been used variously as human nutritional supplements and in dietary prophylaxis and therapy. For example, applications of lipoic acid have included U.S. Pat. No. 5,607,980 (Topical compositions having improved skin); U.S. Pat. No. 5,472,698 (Composition for enhancing lipid production in skin); U.S. Pat. No. 5,292,538 (Improved sustained energy and anabolic composition and method of making); U.S. Pat. No. 5,536,645 (Nutritive medium for the culture of microorganisms); U.S. Pat. No. 5,326,699 (Serum-free medium for culturing animal cells); etc.

[0013] Coenzyme Q or ubiquinone has been used as a medicine or food supplement. For example, uses of ubiquinone include U.S. Pat. No. 6,090,414 (Method and composition to reduce cancer incidence); U.S. Pat. No. 6,086,190 (Food supplements); U.S. Pat. No. 6,080,788 (Composition for Improvement of cellular nutrition and mitochondrial energetics); U.S. Pat. No. 6,080,388 (Cosmetic and dermatological sunscreen formulations); U.S. Pat. No. 6,063,432 (Fruit health bar formulation); U.S. Pat. No. 6,048,846 (compositions used in human treatment); U.S. Pat. No. 6,048,566 (Non-alcoholic beverage and process of making), etc.

[0014] Creatine has enjoyed increasing use as a nutritional additive by athletes. Other uses of creatine are discussed in U.S. Pat. No. 6,093,746 (Therapeutic agents for asthma); U.S. Pat. No. 6,071,962 (Oxa acids and related compounds for treating skin conditions); U.S. Pat. No. 6,060,512 (Method of using hydroxycarboxylic acids or related compounds for treating skin changes associated with intrinsic and extrinsic aging); U.S. Pat. No. 6,013,290 (Assemblage of nutrient beverages and regimen for enhancing convenience, instruction and compliance with exercise supplementation); U.S. Pat. No. 6,008,253 (Use of 3-guanidino propionic acid to increase endurance, stamina and exercise capacity); U.S. Pat. No. 6,008,252 (Method for increasing muscle mass); etc.

[0015] What is needed is an improved nutritional pet food which truly is formulated to meet the needs of older pets. A survey of pet food Web sites uncovered no formula providing carnitine or lipoic acid. Such a pet food would also provide the latest in anti-aging compounds that have been shown to increase energy and stamina, with fewer calories.

SUMMARY OF INVENTION

[0016] It is an object of the present invention to improve pet diets, preferably in pets with deficient mitochondrial metabolism. It is a further object to provide a combination of an effective amount of a suitable antioxidant and an effective amount of a carnitine in a wide variety of foods and food supplements. It is a further object of the present invention to improve the diet of mature dogs, cats, horses, fish, birds and other animals.

[0017] A pet food formulated for senior pets provides α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day. In a preferred embodiment, the carnitine is acetyl-L-carnitine. In a preferred embodiment, the α-lipoic acid is R-α-lipoic acid. In yet another embodiment, the coenzyme Q is coenzyme Q10.

[0018] In another embodiment, there is provided a pet treat for senior pets, the treat formulated so as to provide α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day. In a preferred embodiment, the carnitine is acetyl-L-carnitine. In a preferred embodiment, the α-lipoic acid is R-α-lipoic acid. In yet another embodiment, the coenzyme Q is coenzyme Q10.

[0019] In another embodiment, there is a pet supplement for mature pets, the supplement offering α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day. In a preferred embodiment, the carnitine is acetyl-L-carnitine. In a preferred embodiment, the α-lipoic acid is R-α-lipoic acid. In yet another embodiment, the coenzyme Q is coenzyme Q10.

DETAILED DESCRIPTION

[0020] Pet foods lack four important ingredients: carnitine, lipoic acid, coenzyme Q and creatine. These constituents are essential to discourage aging and provide more energy to older animals and others with unhealthy mitochondria. Recent research has shown precisely how these compounds work to promote healthy mitochondria, which are the energy powerhouses of the cells. Mitochondria are responsible for the production of ATP and are present in relatively high numbers in essentially all cells of the body. The mitochondrial electron transport system consumes approximately 85% of the oxygen utilized by a cell. Cellular energy deficits caused by declines in mitochondrial function can impair normal cellular activities and compromise the cell's ability to adapt to various physiological stresses, a major factor in aging. Because of this high oxygen use, the mitochondria also have the highest production of oxidants.

[0021] Oxidants damage mitochondria in three important ways. Oxidants damage DNA, lipids and protein. The intramitochondrial DNA (mtDNA) have levels of oxidative damage which are at least 10-fold higher than those of nuclear DNA, which correlates with the 17-fold higher evolutionary mutation rate in mtDNA compared with nuclear DNA. mtDNA oxidation accumulates as a function of age, which has been shown in several species, including humans. This may lead to dysfunctional mitochondria. Mitochondrial protein damage is also age-related and may decrease energy production and increase oxidant production. Oxidative damage to mitochondrial lipids contributes to the decreasing fluidity of cell membranes with age. The lipid cardiolipin is a major component of the mitochondrial membrane and facilitates the activities of key mitochondrial inner membrane enzymes. The aged, damaged mitochondrial membrane cannot contain the oxidants, nor can it maintain as high a polarity as the younger membrane.

[0022] Fatty acid oxidation is an important energy source for many tissues. The activity of carnitine-acetyl-carnitine exchange across the inner mitochondrial membrane is of great importance. The activity of this exchange reaction is decreased significantly with age, which may be due to a lower intra-mitochondrial pool of carnitine. L-carnitine or acyl-L-carnitine (ALC) has been shown to slow or reverse this age-related dysfunction. It also can reverse the age-

related decrease in cardiolipin, age-associated decrease in mtDNA transcription, and decreased membrane potential. By itself, L-carnitine or ALC cannot correct the problem of excess oxidants. In fact, it was recently reported that carnitine supplementation increased oxidant production by 30% and decreased cell antioxidants markedly. Thus, ALC administration in older individuals may contribute to greater oxidative stress.

[0023] For the aged mitochondrial engines to run on all cylinders, both carnitine and lipoic acid are essential. Lipoic acid is an antioxidant. And R-α-lipoic acid is a mitochondrial enzyme which can help reverse the decline in metabolism seen with age. R-α-lipoic acid supplementation has been shown to 1) reverse the age-related decrease in oxygen consumption, 2) restore the age-related decline in mitochondrial membrane potential, 3) triple the ambulatory activity of aged rats, 4) significantly lower the age-related increase in oxidants, and 5) restore glutathione and ascorbic acid levels to youthful levels.

[0024] Clearly, both carnitine and lipoic acid contribute to restoration of age-related mitochondria function and metabolic activity in older animals. This contributes to improvements in energy, general health, mental acuity, immune system function, fur appearance and muscle mass.

[0025] Carnitine is available in many forms and all those are included in the invention of the combination of carnitine and thioctic acid. Carnitine and carnitine derivatives have been used as metabolites in animal husbandry and for human diet and therapy. U.S. Pat. No. 5,362,753 (Method of increasing the hatchability of eggs by feeding hens carnitine); U.S. Pat. No. 4,687,782 (Nutritional composition for enhancing skeletal muscle adaptation to exercise training); U.S. Pat. No. 5,030,458 (Method for preventing diet-induced carnitine deficiency in domesticated dogs and cats); U.S. Pat. No. 5,030,657 (L-carnitine supplemented catfish diet); U.S. Pat. No. 4,343,816 (Pharmaceutical composition comprising an acyl-carnitine, for treating peripheral vascular diseases); U.S. Pat. No. 5,560,928 (Nutritional and/or dietary composition and method of using the same); U.S. Pat. No. 5,504,072 (Enteral nutritional composition having balanced amino acid profile); U.S. Pat. No. 5,391,550 (Compositions of matter and methods for increasing intracellular ATP levels and physical performance levels and for increasing the rate of wound repair); U.S. Pat. No. 5,240,961 (Method of treating reduced insulin-like growth factor and bone loss associated with aging); etc. Most preferably, the carnitine is acetyl-L-carnitine.

[0026] A daily dosage of carnitine is about 1 mg to 6 g. Preferably the daily dose of carnitine is 10-1,000 mg. More preferably, the daily dose of carnitine is about 30-500 mg. More preferably, the daily dose of carnitine is at least about 10 milligrams (0.01 g) per day. The daily dose of carnitine also depends on the weight of the pet, which varies widely for adult breeds of dogs and cats. A preferred weight-based daily dosage of carnitine for mature pets is 0.5 to 100 mg/kg/day.

[0027] By lipoic acid or thioctic acid is meant a mitochondrially active antioxidant which physiologically comprises a metabolically reactive thiol group. Mitochondrially active antioxidants including vitamins (especially C, E, B and D), glutathione, N-acetyl cysteine (NAC), lipoic acid, their derivatives, etc., have been used variously as human nutritional supplements and in dietary prophylaxis and therapy. For example, applications of lipoic acid have included U.S. Pat. No. 5,607,980 (Topical compositions having improved skin); U.S. Pat. No. 5,472,698 (Composition for enhancing lipid production in skin); U.S. Pat. No. 5,292,538 (Improved sustained energy and anabolic composition and method of making); U.S. Pat. No. 5,536,645 (Nutritive medium for the culture of microorganisms); U.S. Pat. No. 5,326,699 (Serum-free medium for culturing animal cells); etc. Preferably, the compound is at least one of glutathione, N-acetyl cysteine and lipoic acid. Most preferably, the compound is the R-enantiomeric form of lipoic acid. Metabolites of lipoic acid have been found to have a longer half life and also are suitable for supplementation.

[0028] A daily dosage of lipoic acid is about 5 mg to 8 g. Preferably the daily dose of lipoic acid is 10-1,000 mg. More preferably, the daily dose of lipoic acid is about 30-700 mg. Most preferably, the daily dose of lipoic acid is at least about 40 milligrams (0.04 g) per day. The daily dose of lipoic acid also depends on the weight of the pet, which varies widely for adult breeds of dogs and cats. A preferred weight-based daily dosage of lipoic acid for mature pets is 0.15 to 50 mg/kg/day.

[0029] Q10 is an important supplement. In groups of males and females ranging from 90-106 years, the prevalence of inadequate Q10 status was 40% for women and 24% for men. In women, the decreased Q10 was associated with impaired natural killer cell effectiveness ($p<0.05$), indicating decreased ability to fight infections and quickly eliminate individual cancer cells as they first develop. Q10 also appears to block programmed cell death, or apoptosis, through its action in the mitochondria (Kagan T et al, Ann NY Acad Sci 887:31-47, 1999). Furthermore, Q10 in its reduced from of ubiquinol-10 which is normally present in the blood, appears to protect human lymphocytes from oxidative damage to DNA (Tomasetti et al, Free Radic Biol Med 27 (9-10):1027-32, November 1999). No important adverse effects have been reported from experiments using daily supplements of up to 200 mg Q10 for 6-12 months and 100 mg daily for up to 6 y. Overvad K et al. Eur J Clin Nutr 53(10):764-70, 1999.

[0030] Q10 also may contribute to anti-aging effect by protecting against atherosclerosis which also results from oxidative stress. Pedersen H S, et al. Biofactors 9(2-4): 319-23, 1999). Q10 also improves the tolerance of the senescent myocardium to aerobic and ischemic stress in human atrial tissue and rats. Q10 corrected the age-specific diminished recovery of function in older hearts so that older hearts recovered function at a similar rate to younger ones (Rosenfeldt F L et al. Biofactors 9(2-4): 291-9, 1999).

[0031] As for the supplemental dose of Q10, older Finnish men obtained benefit from 100 mg/day. A woman deficient in Q10 received 150 mg/kg and rapidly improved (Sobriera et al. Neurology 48:1283-43, 1997). Q10 has also been used at dose of about 200 mg/day to help improve heart function in persons with hypertrophic cardiomyopathy. Based on this information, a supplemental dosage for pets ranges from about 0.1 mg/day to about 100 mg/day. The daily dose of coenzyme Q also depends on the weight of the pet, which varies widely for adult breeds of dogs and cats. A preferred weight-based daily dosage of lipoic acid for mature pets is 0.015 to 20 mg/kg/day.

[0032] Because creatine intake is often decreased in older individuals, creatine supplementation should be considered. Many athletes have taken doses of creatine up to 75 grams a day for years without known adverse effects, aside from weight gain, often attributed to increased muscle mass. Creatine may be most beneficial when ingested with glucose, which tends to increase creatine absorption. Often athletes ingest loading doses of 20 g/day divided into four doses for 5 days to one week. Then they take a maintenance dose of 5 g/day. Benefit in one week in older individuals (40-73) has also been seen from a 20 g/day dose, in the form of increased skeletal muscle strength and endurance. It has been reported that 1.5 g-25 g/day are safe for a period of at least a year. A suitable dosage range for pets is about 0.15 g/day to 25 g/day, preferably 0.3-2.5 grams per day and most preferably about 0.5 g/day. On a weight basis, the mature pet would benefit from 15 mg to 1000 mg/kg/day. Creatine is available as a salt, monohydrate, phosphate and citrate.

[0033] In addition to the compositions mentioned above and the examples given below, animal snacks, "treats", and supplements also benefit from the addition of a carnitine and a form of thioctic acid. The carnitine, thioctic acid, and optionally coenzyme Q and/or creatine can be added to bulk powders or dried or canned pet food. The combination of carnitine, thioctic acid, and optionally coenzyme Q and/or creatine can be mixed with any cooked or uncooked food.

[0034] The combination of carnitine, thioctic acid, and optionally coenzyme Q and/or creatine is provided in pet formulations, dried or canned or as a supplement for addition thereto. Animals expected to benefit from the composition include, but are not limited to, dogs, cats, horses, birds and fish.

[0035] The formulations and/or content of these products are on the product label or are otherwise publicly available.

[0036] Additional nutrients are important in older animals, including calcium, vitamin D, Vitamins B12, folic acid, B6, niacin, vitamins C or E, iron and zinc. Many of these nutrients have been found to be deficient in the diets of elders and should be appropriately supplemented along with carnitine, thioctic acid, and optionally coenzyme Q and/or creatine.

[0037] The inventive combination(s) also are conveniently provided in pill or capsule form. A preferred formulation provides lipoic acid and carnitine, optionally in combination with coenzyme Q10 and or creatine, in a timed release formulation to provide a steady supply of the nutrients to the mitochondria which work 24 hours a day. One method of accomplishing timed release is chemically combining the micronutrient(s) with other molecules, which generally slows the process of making the micronutrient(s) available. Also the use of different salts of the micronutrients with different dissolution rates provides for gradual and appropriate release of the product.

[0038] Besides these methods, two other basic systems are used to control release for oral administration: coating a core comprising the micronutrient(s) and excipients (coated system) and incorporating the micronutrient(s) into a matrix (matrix system). Coated systems involve the preparation of product-loaded cores and coating the cores with release rate-retarding materials. Product-loaded cores can be formulated as microspheres, granules, pellets or core tablets. There are many known core preparation methods, including, but not limited to, 1) producing granules by top spray fluidized bed granulation, or by solution/suspension/powdering layering by Wurster coating, 2) producing spherical granules or pellets by extrusion-spheronization, rotary processing, and melt pelletization; 3) producing core tablets by compression and coating with a release rate-retarding material; 4) producing microspheres by emulsification and spray-drying.

[0039] Matrix systems embed the micronutrient in a slowly disintegrating or non-disintegrating matrix. Rate of release is controlled by the erosion of the matrix and/or by the diffusion of the micronutrient(s) through the matrix. In general, the active product substance, excipients and the release rate-retarding materials are mixed and then processed into matrix pellets or tablets. Matrix pellets can be formed by granulation, spheronization using cellulosic materials, or by melt pelletization using release retardant materials, while matrix tablets are prepared by compression in a tablet press. An example of a cellulosic material is hydroxypropylmethyl-cellulose as the release rate retarding material.

[0040] Coated or matrix pellets can be filled into capsules or compression tabletted. The rate of release can be further modified by blending coated or matrix pellets with different release rates of the same product to obtain the desired product release profile. Pellets containing any of lipoic acid, carnitine, coenzyme Q10 or creatine can be blended to form a combination product.

[0041] Convenient assays for the requisite bioactivities are described above or in the references cited herein. For example, cardiolipin content is readily assayed as referenced in Guan, Z. Z., Soderberg, M., Sindelar, P., and Edlund, C. Content and Fatty Acid Composition of Cardiolipin in the Brain of Patients with Alzheimer's Disease. Neurochem. Int. 25: 295-300, 1994 and oxidant production (DCFH) may be assayed as described by LeBel, C. P., Ischiropoulos, H., and Bondy, S. C. Evaluation of the Probe 2',7'-Dichlorofluorescin as an Indicator of Reactive Oxygen Species Formation and Oxidative Stress. Chem. Res. Toxicol. 5: 227-231, 1992. Assays for parameters of aging such as host activity and behavior such as grooming, sexual activity, dominance, coat condition, wound repair, including molecular lesions, muscle strength and tone, kidney appearance and function, etc. are similarly well known in the art.

EXAMPLE 1

[0042] The Eukanuba Senior Maintenance (IAMS) is formulated to help nutritionally stabilize the senior dog's digestive system. The senior maintenance diet was formulated with 50% more antioxidants than their adult formulas, from sources such as vitamin E and Beta-Carotene. This is intended for small breeds over 8 years of age, medium breeds over 7 years of age, large breeds over 6 years of age, and giant breeds over 5 years of age. Its ingredients include chicken by-product meal, corn meal, ground grain sorghum, ground whole grain barley, chicken, fish meal, dried beet pulp (sugar removed), chicken fat (preserved with mixed tocopherols, a source of vitamin E, and citric acid), dried egg product, brewers dried yeast, vitamins and minerals. It provides 4,219 kcal/kg or 350 kcal/cup in the following distribution: protein 27%, fat 28%, and carbohydrate 45%.

Guaranteed Analysis:

Nutrient	(percent)
Crude Protein min.	26.0%
Crude Fat min.	10.0%
Crude Fiber max.	4.0%
Moisture max.	10.0%
Omega-6 Fatty Acids min.	1.75%
Omega-3 Fatty Acids min.	0.25%

[0043] To improve the nutritional value for senior dogs, the following ingredients are added: α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally Q10 at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

EXAMPLE 2

[0044] The Iams Senior Formula for Cats meets most of the special nutritional needs of cats over 7 years of age. Iams Senior Formula provides essential protein levels. And with 30% less fat than Iams Original Formula, the cat avoids excess weight gain. Ingredients include chicken by-product meal, chicken, rice flour, corn meal, dried beet pulp (sugar removed), dried egg product, natural chicken flavor, fish meal, potassium chloride, brewers dried yeast, dl-methionine, calcium carbonate, salt, choline chloride, vitamin E supplement, zinc oxide, chicken fat (preserved with mixed tocopherols, a source of vitamin E, and citric acid), vitamins and minerals. This formulation provides 4,108 kcal/kg, or 373 kcal/cup from the following sources: protein 32%, fat 34%, and carbohydrate 34%.

Guaranteed Analysis:

Nutrient	(percent)
Crude Protein min	32.0%
Crude Fat min	14.0%
Crude Fat max	16.5%
Crude Fiber max	3.0%
Moisture max	10.0%
Ash max	6.75%
Magnesium max	0.099%
Taurine min	0.15%
Vitamin B not less than	200 IU/kg

[0045] To properly supply nutrients to older cats, the following ingredients are added: α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally Q10 at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

EXAMPLE 3

[0046] Kasco® Maintenance Dog Food is a low-protein, low-fat, low-calorie formula for maintenance for less active and older dogs. It contains the following ingredients: Ground yellow corn, poultry by-product meal, poultry fat (preserved with mixed tocopherols), beet pulp, salt, calcium carbonate, dicalcium phosphate, choline chloride, zinc proteinate, vitamin E supplement, ascorbic acid, zinc oxide, manganese proteinate, copper proteinate, extract of rosemary, manganous oxide, copper sulfate, vitamin A acetate, niacin supplement, calcium pantothenate, vitamin B12 supplement, vitamin D3 supplement, pyridoxine hydrochloride, riboflavin supplement, thiamine mononitrate, calcium iodate, biotin, sodium selenite, folic acid. Its guaranteed analysis is crude protein (min) 22%, crude fat (min) 10%, crude fiber (max) 3.5%, and moisture (max) 11%.

[0047] To formulate this product specifically for older dogs, the following ingredients are added: α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally Q10 at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

EXAMPLE 4

[0048] Heinz provides a blend of ingredients called the Custom Fitness™ formula of Cycle Senior. It contains rice and oatmeal; vitamins A, C, and E plus beta-carotene; and no added salt; and limited calcium, phosphorus, and fat. Ingredients of the dry formula include corn, soybean hulls, chicken by-product meal, feeding oat meal, brewers rice, whole wheat, animal fat (BHA used as a preservative), animal digest, condensed grain fermentation solubles, bone phosphate, calcium carbonate, potassium chloride, L-lysine monohydrochloride, L-threonine, D,L-methionine, choline chloride, minerals (ferrous sulfate, zinc oxide, manganous oxide, copper sulfate, calcium iodate, sodium selenite), vitamins (vitamin E supplement, niacin, D-calcium pantothenate, riboflavin supplement, pyridoxine hydrochloride, thiamin mononitrate, vitamin A supplement, folic acid, biotin, vitamin B12 supplement, vitamin D3 supplement), antioxidant blend (ascorbic acid, beta carotene, marigold extract), BHA (preservative), tocopherols (preservative), citric acid (preservative), rosemary extract (preservative).

Dry Formula Guaranteed Analysis

	As Fed	Dry Weight
Protein	19.50%	21.31%
Sodium	0.08%	0.09%
Crude Fat	Not less than 9.00%	
Crude Fiber	Not more than 4.00%	
Moisture	Not more than 12.00%	
Calcium	Not less than 0.60%	
Phosphorous	Not less than 0.50%	
Sodium	Not more than 0.15%	
Calories per cup	350 Calories	

[0049] The canned formula has the following ingredients: water sufficient for processing, chicken, wheat flour, oatmeal, turkey, wheat gluten, brewer's rice, meat by-products, soybean oil, guar gum, vitamins (vitamin E supplement, niacin, D-calcium pantothenate, riboflavin supplement, pyridoxine hydrochloride, thiamin mononitrate, vitamin A supplement, folic acid, biotin, vitamin B12 supplement, vitamin D3 supplement), sodium tripolyphosphate, potassium chloride, titanium dioxide, calcium sulfate, choline chloride, minerals (ferrous sulfate, zinc oxide, manganous oxide, copper sulfate, calcium iodate, sodium selenite), DL-methionine, carrageenan, FD&C yellow 6, iron oxide, antioxidant blend (ascorbic acid, beta carotene, marigold extract), and FD&C yellow 5.

Canned Formula Guaranteed Analysis

	As Fed	Dry Weight
Protein	5.13%	26.50%
Sodium	0.15%	0.77%
Crude Fat	Not less than 3.0%	
Crude Fiber	Not more than 5.0%	
Moisture	Not more than 82.0%	
Calories per cup	288 Calories	

[0050] To convert these products to support the metabolism of active seniors, the following ingredients are added: α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally Q10 at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

EXAMPLE 5

[0051] Mera Dog Sensitive is a maintenance formula suitable for the senior and less active dog. Main ingredients are turkey and rice, which are highly digestible and provide protein with reduced calories. Specifically, ingredients include rice (60%), turkey meat meal (20%), poultry fat, beet fiber, linseed, brewers yeast, minerals, dehydrated egg, poultry meat hydrolysate, DL-methionine, L-lysine. Additives include vitamin A 15,000 I.E./kg, vitamin D3 1.500 I.E./kg, vitamin E 120 mg/kg, and copper 19 mg/kg. Guaranteed Analysis is crude protein 21.0%, crude fat 9.0%, crude fiber 2.5%, crude ash 7.0%, calcium 1.2%, phosphorus 1.0%, and sodium 0.4%.

[0052] To convert this product to support the metabolism of active seniors, the following ingredients are added: α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally Q10 at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

EXAMPLE 6

[0053] NuFood was created for pet owners concerned about giving their dogs top quality nutrition. NuFood is made with 100% pure chicken meat (no by-products) and is prepared to provide a pure, tasty and highly digestible meal. There are no gels, dyes or artificial flavors; and all ingredients are approved for human consumption. The main ingredients are chicken meat, corn, breadcrumbs, and water. Ingredients include 100% pure chicken meat, corn gluten meal, toasted wheat crumbs, propylene glycol, corn syrup solids, wheat flour, corn flour, glucono delta lactone, salt, citric acid, sodium nitrite, seasoning, and water sufficient for processing.

[0054] To convert this product to support the metabolism of active seniors, the following ingredients are added: α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally Q10 at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

EXAMPLE 7

[0055] The Science Diet Canine Senior product described in the Background can benefit from the following additional ingredients: α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally Q10 at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

EXAMPLE 8

[0056] The Canine Senior formula described in the Background can benefit from the following additional ingredients α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally Q10 at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

EXAMPLE 9

[0057] The Science Diet Feline Senior canned fish formula (as well as other Science Diet cat foods) can benefit from the following additional ingredients: α-lipoic acid at about 0.15 to 50 mg/kg body weight/day, carnitine at about 0.5 to 100 mg/kg/day, and optionally Q10 at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

[0058] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

We claim:

1. A pet food formulated for senior pets, the food so formulated as to provide the following chemicals in a daily dosage comprising

a) α-lipoic acid at about 0.15 to 50 mg/kg body weight/day,

b) carnitine at about 0.5 to 100 mg/kg/day, and

c) optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

2. The pet food of claim 1 wherein the carnitine is acetyl-L-carnitine.

3. The pet food of claim 1 wherein the α-lipoic acid is R-α-lipoic acid.

4. The pet food of claim 1, wherein coenzyme Q is coenzyme Q10.

5. A pet treat for senior pets, the treat formulated so as to provide

a) α-lipoic acid at about 0.15 to 50 mg/kg body weight/day,

b) carnitine at about 0.5 to 100 mg/kg/day, and

c) optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

6. The pet treat of claim 5, wherein the carnitine is acetyl-L-carnitine.

7. The pet treat of claim 5, in which the α-lipoic acid is R-α-lipoic acid.

8. The pet treat of claim 5, wherein coenzyme Q is coenzyme Q10.

9. A pet supplement for mature pets, the supplement offering

a) α-lipoic acid at about 0.15 to 50 mg/kg body weight/day,

b) carnitine at about 0.5 to 100 mg/kg/day, and

c) optionally coenzyme Q at about 0.01 mg/kg/day and/or creatine at about 15 mg to about 1 g/kg/day.

10. The supplement of claim 9 wherein the carnitine is acetyl-L-carnitine.

11. The supplement of claim 9 wherein the α-lipoic acid is R-α-lipoic acid.

12. The supplement of claim 9, wherein the coenzyme Q is coenzyme Q10.

* * * * *

EXHIBIT H

US006503506B1

(12) **United States Patent**
Germano

(10) **Patent No.: US 6,503,506 B1**
(45) **Date of Patent: Jan. 7, 2003**

(54) **NUTRIENT THERAPY FOR IMMUNO-COMPROMISED PATIENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(51) **Int. Cl.**[7] **A61K 38/44**
(52) **U.S. Cl.** **424/94.3**; 514/561
(58) **Field of Search** 424/94.3; 514/561

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,045,809 A 4/2000 Postaire et al. 424/400

Primary Examiner—Jean C. Witz
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(57) **ABSTRACT**

A nutritional supplement is taught for treating chronic debilitating diseases such as HIV/AIDS to overcome conditions of oxidative stress, decreased lean muscle mass, decreased energy production (mitochondrial failure) and support immune function. It comprises orally administrable superoxide dismutase (SOD), preferably SOD/GLIADIN, in combination with other antioxidant/immune support components (Beta Glucans, Nucleotides, Fruit Polyphenols); High Immunoglobin Whey; (undenatured whey), Ornithine alpha ketoglutarate (OKG), Branched Chain Amino Acids and Glutamine to reduce loss of lean muscle mass; and Coenzyme Q 10, D-Ribose and L-Carnitine to provide energy support (decrease mitochondrial failure).

11 Claims, No Drawings

NUTRIENT THERAPY FOR IMMUNO-COMPROMISED PATIENTS

BACKGROUND OF THE INVENTION

Unfortunately there appears to be a growing number of people suffering from chronic debilitating diseases characterized by muscle tissue wasting, decreased energy and oxidative stress and immune impairment.

Most dramatic of such disease is the major increase in HIV presently infecting over 50 million people. Currently approximately 22 million people have died from the consequences of HIV induced Acquired Immune Deficiency Syndrome (AIDS). HIV attacks the human immune system, weakening the body and reducing the patient's ability to ward off opportunistic infections, ultimately rendering him/her defenseless against diseases that usually and under normal circumstances can be successfully treated. There is no cure for AIDS.

Over the years a sizable array of vaccines, antiretroviral drugs, such as AZT and other viral suppressive compounds, have been developed that seek to—if not defeat, at least control the rate at which HIV replicates and thereby slow the progression of the disease, or even arrest it. However, most of these drugs to be effective have to be taken in combination with complicated regimes that need to be followed meticulously and indefinitely. More importantly, the toxic nature of these drugs leads to further decreases in host defense, energy production and increases in oxidative stress furthering the development of the disease. These drugs are expensive and not affordable by many if not most HIV infected persons. Furthermore, even if available and affordable, there presently are no reliable data on the side effects of such long term therapy, or HIV's capacity to mutate into drug resistant strains.

To those infected with AIDS and many other chronic debilitating diseases, wasting syndrome is a very real part of their every day life. Wasting is the term used for the loss of lean muscle mass due to the virus placing additional nutritional demands on the body. These stresses can diminish appetite causing the body to use protein and other nutrients from muscle stores that help the body function correctly. As a result of this, muscles become smaller, weaker and less flexible. Eventually when muscle loss becomes significant, the ability for the body to function normally and combat other common infection greatly diminishes.

In recent years, a considerable amount of information on the spectrum of clinical consequences of HIV infection has been accumulated. The most striking characteristics of this disease include severe malnutrition and wasting syndrome. Such malnutrition involves both changes in overall body composition as well as deficiencies of specific nutrients. As HIV infection progresses to AIDS, a significant result is under-nutrition producing the added effects of starvation, a potent immuno-suppressant. Nutritional support could thus help maintain health in the HIV+ patient by replacing lost nutrients, compensating for nutritional damage done by the retrovirus-induced immunodeficiency, and stimulating the remaining immune system and cells for better host defenses. The medical community generally agrees that there remains an urgent need for interventions, including inexpensive nutrient therapies, which serve as an adjunct to current medical treatment for persons with HIV/AIDS (PWAs).

It has been shown that the course of infection is influenced by different factors including age, genetics, environmental, opportunistic infections, therapy and nutritional status.

Among these, there is considerable evidence to suggest important links between nutrients, oxidative stress and HIV infection. Alterations of nutrients and increased oxidative stress associated with inadequate antioxidant intake have been observed in HIV infected subjects. Such nutrient depletions may influence immunological function, viral replication, carcinogenesis, development of cardiomyopathy and resistance to infection.

Additionally adherence is also an extremely important issue for nutritional supplements. If the product is distasteful or unpleasant to consume its use will not be repeated.

Unfortunately, there currently is no nutritional supplement on the market that addresses these major issues and conditions, such as oxidative stress, decreased lean muscle mass and weight, and mitochondrial failure (decreased energy production), associated with HIV/AIDS and other chronic debilitating diseases.

BRIEF DESCRIPTION OF THE INVENTION

The present nutritional support composition addresses the needs of those whose immune systems are compromised through HIV/AIDS and other chronic debilitating diseases through a multiprong approach designed to:

Decrease oxidation stress

Help restore lean muscle mass

Up-regulate/increase energy production (decrease mitochondria failure)

Support Immune System

Specifically the present composition comprises in combination:

1. Orally administrative superoxide dismutase (hereinafter referred to as SOD) in combination with a lipid or protein carrier derived from plants to serve as an antioxidant support.

Particularly preferred is the protein prolamine derived from cereals, and especially SOD/Gliadin.

The orally administrable SOD component may be supplemented by other antioxidant components—Beta Glucans, Nucleotides and Fruit Polyphenols.

2. A mitochondrial/energy support component selected from the group consisting of Coenzyme Q10, D-Ribose and L-Carnitine

3. A component for maintaining lean muscle mass comprising a member of the group Ornithine alpha ketoglutarate (OKG) and High Immunoglobulin Whey (undenatured whey), which may be supplemental by other components such as Branched Chain Amino Acids, Instantized Casein, and Glutamine.

In addition to the foregoing functions, SOD/Gliadin, Beta Glucans, Coenzyme Q10, Nucleotides, Glutamine and Undenatured Whey Protein also help to support immune function.

The present composition will not interfere with or react with current drug therapies for treating HIV/AIDS or cancer. It is easily miscible with water, milk or juices to completely dissolve. It is easily blendable with flavoring agents to overcome poor adherence plaguing other nutritional products. Flavors such as Dutch Chocolate, Wild Berry and Vanilla Honey Caramel have been produced.

While certain of the above components have been used therapeutically, the present invention distinguishes over such prior art by:

Providing a multicomponent system approach to treating chronic debilitating diseases, and

Providing the first orally bioavailable form of SOD in combination with other synergistic nutritional components

DETAILED DESCRIPTION OF THE INVENTION

1) Antioxidant Support

The primary agent is orally administrable superoxide dismutase (SOD) in combination with a lipid or protein carrier derived from plants. A detailed description of such an antioxidant will be found in U.S. Pat. No. 6,045,809 issued Apr. 4, 2000 whose specification is hereby incorporated by reference. Such SOD compositions have good bioavailability and are therefore therapeutically effective.

In one embodiment the proteins are selected form the group consisting of prolamines and polymer films based on prolamines. The prolamines are preferably of vegetable origin and can be obtained from different cereals, especially wheat, rye, barley, oats, rice, millet and maize. Particularly preferred is gliadin derived from wheat. SOD/Gliadin, which has recently become available commercially, is especially preferred in the instant composition.

In another embodiment, the plant lipids are preferably selected from the group consisting of ceramides, phospholipids tylacoids and diacylglycerols. Particularly desired are ceramides of vegetable origin derived from cereals, especially wheat.

SOD (Superoxide Dismutase)

In the past, SOD was a very popular supplement acting as a master cellular defense enzyme. Unfortunately, taking this supplement orally yielded little if any benefit since it is easily destroyed in the GI tract via digestive enzymes. Hence, the use of injectable SOD from bovine sources was the form of choice in most of the published studies. Today, after extensive research and development, SOD microencapsulated with Gliadin (SOD/Gliadin) has been shown to be absorbed intact orally as well as up-regulate other defense enzymes in the cell: Much of the research available on SOD and the immune system centers on HIV and antioxidants. Because the immune system has a more general function in the body, protecting us from disease and keeping us healthy in a myriad of ways, the clearest observations of the relationship between free radicals, SOD and immune system are found in studying HIV and AIDS. But research also makes associations between oxidative stress and the overall strength of the immune system. It has been found that SOD can offset the damage done by free radicals, prevent damage to the immune system, and consequently help delay or prevent the onset of degenerative diseases and immune-related conditions like HIV and AIDS.

Studies show that:

Adding SOD to infected white blood cells from patients with HIV showed that SOD slowed down the spread of HIV through the infected cells. The reducing effect of SOD on superoxide seems to affect not only the level of IIIV in the white blood cells, but also the rate of transmission of the virus between cells.

SOD may slow the expression of HIV to AIDS by demonstrating that SOD reduced the levels of the virus core protein, an indicator of its presence in the cells.

SOD can enhance immunity. The presence of free radicals appears to contribute to the suppression of the immune system. As part of the immune response free radicals like superoxide are produced, but these free radicals can cause tissue and immune system damage. SOD can counter the effects of free radicals, thereby enhancing immune function.

Additional antioxidant support compounds (termed AASC for convenience) may also be present in the instant compositions. Such AASC compositions are selected from the group consisting of Beta Glucans and Fruit Polyphenols. The latter are polyphenolics from prune, apple, cherry, pomegranate and nectarine.

Beta Glucans

Our immune system is our primary natural defense against disease and aging. Beta Glucans are fuel for our immune system. Specifically, beta-1,3-D-glucans are unique ingredients derived from yeast cell walls and oats. Once activated by Beta-1,3-D-glucans, the immune system creates "an arsenal of defense" against viral, bacterial, fungal, parasitic or neoplastic assailants. Unlike other immune enhancing supplements and pharmacological drugs, beta-1, 3-D-glucans, trigger the immune response selectively where and pharmacological drugs, beta-1,3-D-glucans, trigger the immune response selectively where it starts-at the macrophage. Macrophages play an essential and pivotal role in the initiation and maintenance of the immune response.

Beta Glucans work by activating the macrophages, or immune cells, which trap and engulf foreign substances. Also, the activated cells start a cascade of events that cause the entire immune system to be alerted and mobilized, in an entirely naturally activated sequence. Beta Glucans also have powerful antioxidant attributes, with heightened free-radical scavenging activity to nutritionally enable the immune system to fight back against health invaders (pathogens) such as fungus, bacteria, viruses and parasites. While Beta Glucans can be derived from yeast and grain sources, activation of the immune response is best achieved from yeast cell wall and oat Beta Glucans.

Fruit Polyphenols

Polyphenolic Flavonoids (polyphenols) are compounds found in fruits, vegetables, tea, beans, and grains. Many of the flavonoid substances are known as "bioflavonoids". Polyphenolic flavonoids are very powerful antioxidants. Acting as antioxidants means that these flavonoids can help neutralize or inactivate free radicals before they damage the cells within the human body. Free radicals are natural by-products of daily metabolism and contribute to the aging process. Polyphenolic flavonoids have the following properties: immune-stimulating, anti-viral, anti-inflammatory, anti-mutagenic, cardio-protective, anti-allergic, and anti-carcinogenic. The anti-cancer activity of polyphenols has been correlated with the inhibition of colon, esophagus, lung, liver, breast and skin cancers.

2) Mitochondrial/energy Support

Key ingredients for providing this result are Coenzyme Q10, D-Ribose and L-Carnitine.

Coenzyme Q10

Coenzyme Q10 is an essential component of cellular energy production and respiration by participation in the mitochondrial electron transport system, which supplies energy (ATP) for a variety of physiological functions. Virtually every cell of the human body contains coenzyme Q10. Muscle mitochondria lack adequate coenzyme Q10 in people several degenerative diseases—from Alzheimer's to HIV/AIDS.

Additionally, COQ10 plays an important role in the preserving a healthy functioning immune system and modulates immunity. Blood levels of Coenzyme Q10 are founds to be low in individuals with HIV infection or AIDS. It is known that HIV/AIDS individuals have a deficiency of COQ10 and the deficiency increased with the severity of the disease. Human studies have demonstrated that COQ10 increases IgG and T4-lymphocytes when administered orally—clinically relevant for cancer, HIV/AIDS and other infectious diseases. Studies have shown that COQ10 has a positive influence on the host defense system. The T4/T8

ratios of lymphocytes are known to be low in patients with AIDS, ARC and malignancies. Oral administration of COQ10 revealed a positive increase in T4/T8 rations in HIV patients.

Individuals with HIV are characterized by both significant mitochondrial alterations and a dramatic tendency to undergo apoptosis. Coenzyme Q10 is an important antiapoptotic agent with promising potential for HIV therapy given the recent findings of apoptosis involvement toward AIDS progression of HIV infected individuals. Lastly, it has been shown that the antiviral nucleoside analogue zidovudine (AZT) depletes levels of mitochondrial DNA in muscle of patients on long-term therapy. Hence, COQ10 represents a critical therapeutic agent that may prevent neuronal mitochondrial dysfunction and apoptosis beneficial in the prevention of neurodegenerative processes in AIDS patients.

L-Carnitine

L-carnitine is an amino acid abundantly found in skeletal muscle. It functions primarily to regulate fat metabolism and also acts as a carrier of fatty acids into the mitochondria, where they are oxidized and converted into energy (ATP). Hence, it has the potential to improve mitochondrial function, fat metabolism, endurance and enhance the normal functioning of the heart. It has been established in the literature that serum Carnitine deficiency is common in patients with HIV/AIDS especially those on certain medications. AZT as used in the treatment of AIDS, causes mitochondrial myopathy. Additionally, since AZT is associated with mitochondrial destruction and impairment of mitochondrial DNA synthesis crucial to the pathogenesis of the disease, L-carnitine becomes a critical part of the nutritional support plan. The depletion of Carnitine which regulates the metabolism and function of peripheral nerves and mitochondrial DNA synthesis could contribute to the neurotoxicity of certain medications used to treat the disease as well as apoptosis and other significant symptoms. The depletion also is attributed to the clinical symptoms of myalgia and muscle weakness associated with the disease. Because Carnitine status is an important contributing factor to immune function in patients with AIDS, L-carnitine supplementation could have a role as a complimentary therapy for HIV infected individuals.

Ribose

Ribose is a carbohydrate, or sugar, used by all living cells and is an essential component in our body's energy production. As a new nutraceutical Ribose helps the body naturally restore its energy level. It's used by the body's cells to form the primary source of all the body's energy—ATP. ATP, the body's primary energy-carrying molecule, is necessary for maintenance of cellular integrity and function. Ribose plays a key role in the generations and recovery of ATP. Since cells and organs need adequate energy in order to maintain integrity and function, it is essential that the supply of ATP be replenished soon after it is consumed. Ribose provides benefits by quickly restoring energy levels in heart and skeletal muscles. Numerous studies demonstrate the ability of ribose to increase ATP levels and total adenine nucleotide recovery promoting skeletal and cardiac muscle energy metabolism. Since ATP production is hampered via mitochondrial dysfunction typically seen in AIDS, Ribose offers powerful complimentary support to other nutrients addressing energy depletion.

In addition to the foregoing components, supplemented effect is obtained by the added presence of Glutamine and SOD/Gliadin (also present due to their antioxidant effect), as well as medium chain triglycerides.

3) Agents for Maintaining Lean Muscle Mass

The key component for affecting this result is Ornithine Alpha Ketoglutarate (OKG).

Ornithine Alpha-Ketoglutarate

The amino acids Ornithine and glutamine are combined to form Ornithine Alpha-Ketoglutarate (OKG). Ornithine Alpha-Ketoglutarate affects human metabolism through three primary mechanisms: as an anabolic agent (releasing Human Growth Hormone, HGH), as an anti-catabolic agent, and as an inducer of protein synthesis. All three mechanisms contribute to muscular development and enhanced recovery. OKG has been used to treat patients suffering from burns, surgery, malnutrition and other trauma. Although the precise mechanism's unknown, OKG treatment decreases muscle protein catabolism (breakdown) and/or increases protein synthesis, in addition to promoting wound healing. OKG may promote the secretion of anabolic hormones such as insulin and growth hormone and increase amino acid metabolism (glutamine & arginine), which may help explain some of the clinical findings.

OKG supplements have been shown to improve protein retention, would repair, and immune function in hospitalized patients partly by increasing levels of anabolic (growth-promoting) hormones such growth hormone.

In addition to OKG, other agents for restoring lean muscle mass may be incorporated in the present compositions. Examples thereof are Undenatured Whey Protein, Instantized Cascin and Branched Chain Amino Acids. The Nucleotides and Glutamine used for antioxidant support also contribute to restoring muscle mass.

Whey Protein

AIDS wasting is characterized by a loss of lean body mass including muscle and organ tissue, coupled with increased fat production. Loss of lean body mass can lead to muscle weakness, organ failure and sometimes death, making AIDS wasting a leading contributor to HIV related deaths. When it comes to nutritional support directed at maintain lean mass adequate calories and good quality protein are essential.

Whey protein concentrate has long been a favorite of body builders because it is the best protein for tissue repair and muscle building. The most commonly used criterion to measure quality of a protein in Biological Value (BV), which is the amount of nitrogen (body protein in grams) replaceable by 100 grams of protein in the adult diet. The higher its protein's BV, the higher its nitrogen retention. Proteins with the highest BV are the most potent lean tissue sparing and growth promoting proteins.

Whey is a complete protein, which contains all the essential and non-essential amino acids, and boasts the highest branched chain amino acid content found in nature. Whey also has the highest BV of any available protein. It also appears to have a unique composition of immunomodulating fractions such as immunoglobulins. Using an advanced low temperature filtrations system our undenatured whey and our whey protein is superior in quality.

Branched Chain Amino Acids

In nature, there are three Branched Chain Amino Acids: L-Isoleucine, L-Leucine and L-Valine. Amino acids are the building blocks of protein. These three are among those considered "essential" because they cannot be manufactured in the body and must be obtained through diet. They have been shown to provide safe nutritional support for individuals seeking optimal lean muscle mass. BCAA's play a principle role in muscle recovery, muscle growth and energy maintenance and must be present in the muscle cells to promote protein synthesis. They help increase the bioavailability of complex carbohydrate intake and are absorbed by the muscle cells for anabolic muscle building activity. There is some encouraging evidence suggesting BCAA supplementation may have beneficial effects on fatigue prevention

and enhancing recovery and adaptation. Why we need these special amino acids is simple: scientific evidence shows that branched-chain amino acids may help restore muscle mass following surgery, an injury, or trauma. They also help in people who have liver disease. A general deficiency of protein in the diet can cause a loss of stamina, lowered resistance to infection, slow healing of wounds, weakness, and depression.

Glutamine

Glutamine is the most abundant amino acid in the body. It is crucial for many aspects of healthy body function including maintenance of optimal antioxidant status, building and maintenance of muscle tissue, maintenance of optimal immune function, and repair and maintenance of intestinal tissue. L-Glutamine is highly correlated to muscle protein synthesis. It appears that during stress, whether inflicted on the body through heavy exercise, severe illness or a (viral) infection the body's glutamine requirements increase considerably. With the short-term metabolic stress that is created by acute infections, the body can soon return to normal rates of glutamine use. The muscle glutamine levels are quickly restored and the muscles are not damaged. Unfortunately, with the continuous metabolic stress that results from the chronic infection of HIV disease, the demand for glutamine continues and the concentration of this amino acid in the muscles falls rather rapidly. This results in a decline in the synthesis of muscle tissue and, eventually, a wasting away of the muscles. This, of course, makes glutamine crucial for the prevention of internal decline and wasting. A growing body of evidence suggests that the body's defense system requires increasing amounts of glutamine during stress to respond to health threatening events. In the long term low plasma and muscle glutamine levels may lead to net muscle protein loss and decreased resistance against infections. During an immune response when the immune cells have to increase in number and do their work of destroying pathogens, the rate at which glutamine is used increases dramatically. When the body's supply of glutamine runs short, immune function is compromised. Glutamine also increases the activity of natural killer cells and improves the function of neutrophils. In addition, glutamine is critical for the immune function of the respiratory tract, the genitourinary tract, and the intestinal tract.

Nucleotides

Nucleotides are naturally occurring compounds that are involved in key metabolic processes including energy metabolism and enzymatic reactions. They are the building blocks of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Essentially, nucleotides are required by all cells, and are particularly important for cells with rapid turnover including mucosal cells, lymphocytes and macrophages. During stress states, a dietary source is required to promote optimal tissue growth and replication of T-cells. Dietary sources of preformed nucleotides seem to be important for optimal function of the cellular immune response. It has been reported that the absence of dietary nucleotides causes a significant decrease in many specific and non-specific immunologic responses. Nucleotide supplementation has been shown to improve immune function, promote the growth of healthy bacteria in the gut and suppress the growth of gram-negative bacteria in the large intestine. Research in humans and animals has shown that diets lacking dietary nucleotides result in increased susceptibility to infectious agents such as *Candida albicans* and *Staphylococcus aureus*, and may increase risk for gastrointestinal infections.

As problems continue to arise with antibiotic-resistant microorganisms, it will become more important for people to strengthen their immune defense system. Nucleotides represent a critical component in the arsenal.

In addition to the key components of the present invention, a conventional blend of vitamins and minerals can be incorporated. Other conventional ingredients to nutrient drinks may be added.

The range of components in the compositions of the present invention are set for in the Table A below:

All values are on a per daily basis. U stands for units of activity.

TABLE A

	COMPONENT RATIOS	
	BROAD RANGE	PREFERRED RANGE
ANTIOXIDANTS		
SOD lipid or protein carrier	25 U to 5,000 U SOD	200 U to 500 U SOD
OR		
SOD/Gliadin (preferred)	25 U to 5,000 U SOD	200 U to 500 U SOD
Beta Glucans	50 mg to 500 mg	100 mg to 300 mg
Fruit Polyphenols	25 mg to 500 mg	25 mg to 100 mg
Mitochondrial/ Energy Support		
D-Ribose	1,000 mg to 5,000 mg	1,000 mg to 3,000 mg
L-Carnitine	250 mg to 2,000 mg	300 mg to 1,000 mg
Coenzyme Q 10	60 mg to 500 mg	60 mg to 200 mg
Agents to Maintain Lean Muscle Mass		
Ornithine Alpha ketoglutarate	1,000 mg to 8,000 mg	2,000 mg to 5,000 mg
Undenatured whey protein	5,000 mg to 40,000 mg	15,000 mg to 25,000 mg
Branched Chain Amino Acids	1,000 mg to 10,000 mg	3,000 mg to 5,000 mg
Nucleotides	100 mg to 1,000 mg	100 mg to 500 mg
Glutamine	500 mg 1,000 mg	1,000 mg to 5,000 mg

EXAMPLE

The following formulation was blended by conventional blending processes to yield the following composition (on a per day consumption basis). Typically, two one-bottle servings each containing 50% of the defined amounts are taken by the patient.

Component	Per Day Amount (mg)
SOD (as SOD/Gliadin)	*400 →
NUCLEOTIDES (as Cytidine, Adenosine, Guanosine and Uridine Monophosphate)	200
OKG (Ketoglutarate Ornithine)	3,500 ← OKG
Glutamine (as L-Glutamine)	1,000
Beta Glucans (Oat Bran)	200
Coenzyme Q 10	150
Carnitine (L-Carnitine Fumarate)	600
Ribose (D-Ribose)	1,500
LEUCINE (L-LEUCINE)	2,000
VALINE (L-VALINE)	750
ISOLEUCINE (L-ISOLEUCINE)	750

-continued

Component	Per Day Amount (mg)
LYSINE (L-LYSINE)	500
MCT (Medium Chain Triglycerides)	500
Fruit Polyphenols (Apple, Cherry, Nectarine, Prune, Pomegranate	25
LECITHIN (Phosphatidyl Lecithin)	500

*It is 400 units of SOD activity not mg as listed above.

The composition may also contain conventional supplements of Vitamins A, B_6, B_{12}, C, D, E; Thiamine, Riboflavin, Niacin, Folic Acid, Calcium, Iron, Iodine, Magnesium, Zinc, Selenium, Copper, Chromium, Sodium and Potassium; as well as natural and artificial flavors, vegetable and xanthen gums, undenatured Whey Protein Isotate, etc.

While particular embodiments of the invention have been described, various modifications thereof may be made without departing from the spirit of the present invention and without departing from the invention as claimed.

I claim:

1. A nutritional supplement for treating chronic debilitating diseases to overcome conditions of oxidative stress, lean muscle mass loss and decreased energy comprising in combination:

1) an orally administrable superoxide dismutase (SOD) in combination with a carrier derived from plants selected from the group consisting of lipids and proteins,

2) a mitochondrial/energy support component and

3) Ornithine Alpha Ketoglutarate to decrease lean muscle mass loss.

2. The nutritional supplement of claim 1, wherein SOD is in combination with a protein prolamine carrier derived from cereal.

3. The nutritional supplement of claim 1, wherein SOD is in combination with Gliadin.

4. The nutritional supplement of claim 1, wherein component 2) is selected from the group consisting of D-Ribose, L-Carnitine , and Coenzyme Q10.

5. The nutritional supplement of claim 2, wherein component 2) is selected from the group consisting of D-Ribose, L-Carnitine and Coenzyme Q10.

6. A nutritional supplement for treating chronic deliberating diseases to over come conditions of oxidative stress, lean muscle mass loss and decreased energy comprising, in combination, effective amounts of:

1) an orally administrable superoxide dismutase (SOD) in a Gliadin carrier,

2) a mitrochondrial/energy support component selected from the group consisting of D-Ribose, L-Carnitine, and Coenzyme Q10, and

3) Ornithine Alpha Ketoglutarate to decrease lean muscle loss.

7. The nutritional supplement of claim 6 which contains on a daily dosage basis 200 U to 500 U of SOD.

8. The nutritional supplement of claim 6 where component 1) further contains an antioxidant selected from the group consisting of Beta Glucans, Nucleotides and Fruit Polyphenols.

9. The nutritional supplement of claim 6, wherein component 3) further contains a member of the group consisting of Undenatured Whey Protein, Instantized Casein and Branched Chain Amino Acids.

10. The nutritional supplement of claim 6, which further contains a flavoring agent and is readily miscible in water and/or milk.

11. The nutritional supplement of claim 6, which contains on a daily dosage basis:

200 U to 500 U of component 1),

300 to 1,000 mg of component 2), and

2,000 to 5,000 mg of component 3).

* * * * *

EXHIBIT I

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(54) COMPOSITIONS AND METHODS FOR PREVENTION AND TREATMENT OF CHRONIC DISEASES AND DISORDERS INCLUDING THE COMPLICATIONS OF DIABETES MELLITUS

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(57) ABSTRACT

This invention relates to nutrient and therapeutic compositions for treatment and prevention of symptoms and disease conditions associated with microangiopathy and macroangiopathy and to methods using the compositions. In particular, the invention relates to compositions useful in the treatment of diabetic retinopathy and nephropathy, to compositions useful in the treatment of other retinal disorders including macular degeneration and cataracts, to compositions useful in wound healing, to compositions useful for treatment and prevention of neuropathy, to compositions useful for treatment and prevention of cardiovascular disease and to compositions useful for the treatment and prevention of dental and periodontal disorders.

COMPOSITIONS AND METHODS FOR PREVENTION AND TREATMENT OF CHRONIC DISEASES AND DISORDERS INCLUDING THE COMPLICATIONS OF DIABETES MELLITUS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 09/018,273, filed Feb. 4, 1998 which claims priority to U.S. Provisional application Ser. No. 60/037,084, filed Feb. 4, 1997 and Ser. No. 60/043,262, filed Apr. 17, 1997, all of which are incorporated by reference in their entirety herein.

FIELD OF THE INVENTION

[0002] This invention relates to the use of nutrient and therapeutic compositions to ameliorate the disease symptoms and conditions associated with vascular and capillary disorders: microangiopathy and macroangiopathy. Compositions of this invention include antioxidants, neovascular regulators, promoters or cofactors involved in collagen synthesis, as well as vitamins and minerals to supplement deficiencies.

BACKGROUND OF THE INVENTION

[0003] Vascular degeneration, both macroangiopathy and microangiopathy (capillary degeneration), is believed to be the root cause of a variety of degenerative disease conditions that effect a substantial portion of the population. Vascular degeneration is directly associated with cardiovascular disease, atherosclerosis and plaque deposition and indirectly associated with degenerative conditions of the retina (including retinopathy), kidney (nephropathy) and nervous system (neuropathy), as well as skin ulcers.

[0004] A broad variety of treatments have been proposed for conditions associated with microangiopathy, particularly for retinopathy, nephropathy, neuropathy and skin ulcers. Similarly, a variety of treatments and preventive formulas have been proposed for cardiovascular disease. These treatments have met with limited or no success. In some cases, allergic reactions, side effects, drug interactions, or the impracticality of drug therapy have posed serious problems.

[0005] There is clearly a serious and substantial need for methods of treatment which slows or reverses, even temporarily, the onset of symptoms as described above which affect such large numbers of people. There is also clearly a need for methods for preventing the onset or worsening of such conditions.

[0006] The present invention is directed to nutrient and therapeutic compositions for the treatment and prevention of disease conditions associated with vascular and capillary degeneration. The compositions provided herein are useful in treating a variety of conditions including: cardiovascular disease, disease of the retina, nephropathy, and neuropathy. Compositions of this invention are also useful in wound treatment and in the treatment and prevention of dental and periodontal disease. Retinopathy, nephropathy, neuropathy, recurrent, slow-to-heal wounds, and gum disease and tooth loss are complications of diabetes. Formulas of this invention include those that are specifically formulated to improve diabetic complications.

[0007] Compositions of this invention include antioxidants, neovascular regulators, factors that promote or stimulate collagen synthesis and provide nutrients, vitamins and other components to provide nutritional balance. Additional components provide benefit to diabetics. These compositions are directed to the improvement of symptoms and disease conditions by correcting vascular degeneration and by maintaining healthy vascular and capillary tissue.

[0008] The multi-component compositions and methods of treatment of this invention differ from previous proposed treatments in that they are intended to simultaneously ameliorate multiple related factors that are believed to contribute to the disease conditions. Most previous therapeutic compositions for treatment of diabetic complications, including retinopathy and nephropathy, have attempted to treat only one aspect of the disease state.

SUMMARY OF THE INVENTION

[0009] This invention relates to the use of nutrient and therapeutic compositions to ameliorate disease conditions, symptoms and disorders resulting, at least in part, from tissue and cell damage due to oxidative stress and the breakdown of collagen in tissues. In particular, the nutrient and therapeutic compositions of this invention are useful in the prevention and treatment of symptoms and disease conditions associated with vascular and capillary impairment, including macroangiopathy and microangiopathy. The invention specifically provides compositions and methods for the prevention and treatment of diabetic complications, retinopathy, nephropathy, neuropathy, cardiovascular disorders and diseases, slow-to heal or recurrent wounds and gum and tooth disorders including periodontal disease. All of these disorders are believed to share common etiological factors, so that compositions containing related ingredients are effective for treatment and/or prevention of these disorders and conditions.

[0010] In a specific embodiment the present invention provides therapeutic and nutrient compositions and treatment methods using those compositions for ameliorating conditions and symptoms associated with microangiopathy, particularly the complications of diabetes mellitus associated with microangiopathy. More particularly, the methods and compositions of this invention are useful in the amelioration and treatment of diabetic retinopathy and nephropathy. The methods and compositions of this invention are further useful in the treatment of other degenerative ocular conditions such as macular degeneration, cataracts and glaucoma.

[0011] In another specific embodiment, the present invention provides therapeutic and nutrient compositions and treatment methods using those compositions for wound healing, also providing for treatment of recurring and/or slow-to-heal wounds, including among others the treatment of decubitus ulcers. Compositions of this invention can be administered by a variety of routes to an individual having slow-to-heal or recurrent wounds, preferred compositions are for oral administration. The invention also provides wound healing formulations for topical application to wound sites, particularly in the form of ointments. Nutrient compositions useful for prevention of wound development, or for preventing recurrence of slow-to heal wounds in an individual at risk for development of such wounds are also

provided. The formulas provided herein for wound healing include those that are adapted for use by diabetics to provide additional benefits for the treatment or prevention of diabetic complications.

[0012] In a third specific embodiment, the present invention provides therapeutic and nutrient compositions and treatment methods using those compositions for the symptoms and disease conditions associated with neuropathy. Compositions of this invention can be administered by a variety of routes to an individual having neuropathy, preferred compositions are for oral administration. The invention also provides formulations for topical application for relief of the symptoms of neuropathy, including pain relief. Nutrient compositions useful for prevention of neuropathy or for preventing recurrence of symptoms of neuropathy in an individual at risk for development of such symptoms is also provided. The formulas provided herein for neuropathy include those that are adapted for use by diabetics to provide additional benefits for the treatment or prevention of diabetic complications.

[0013] In a fourth specific embodiment, therapeutic and nutrient compositions and treatment methods using those compositions are provided for conditions associated with macroangiopathy (vascular degeneration), particularly for the treatment of cardiovascular disease. Compositions of this invention can be administered by a variety of routes to an individual having symptoms and conditions associated with macroangiopathy, preferred compositions are for oral administration. Nutrient compositions for the prevention of cardiovascular disease are provided. The formulas provided herein for cardiovascular disease include those that are adapted for use by diabetics to provide additional benefits for the treatment or prevention of diabetic complications.

[0014] In yet another specific embodiment, therapeutic and nutrient compositions and treatment methods using those compositions are provided for dental and periodontal disease. Compositions of this invention can be administered by a variety of routes to an individual having symptoms and conditions associated with tooth and gum disease, preferred compositions are for oral administration. Nutrient compositions for the prevention of tooth and gum disease are provided. The formulas provided herein for dental and periodontal disease include those that are adapted for use by diabetics to provide additional benefits for the treatment or prevention of diabetic complications.

[0015] The compositions of this invention combine components which control oxidative stress, provide for appropriate neovascular regulation, provide factors necessary for stimulation or promotion of collagen synthesis and vascular tissue restoration, and preferably improve nutrient, e.g., mineral and vitamin, balance in an individual having conditions or symptoms associated with microangiopathy, particularly for those having diabetic complications and more particularly for those having diabetic retinopathy and/or nephropathy. Nutrients, vitamins and cofactors are provided at least in part to compensate for nutrient spillage that is typically observed in diabetes and the elderly. Preferred combinations of antioxidants and neovascular regulators include combinations of a plant extract providing antioxidant effect comprising bioflavanoids, e.g., proanthocyanidins, with a neovascular regulator selected from the group genistein, daidzein, soy isolate (a specific source of genistein and/or daidzein), cartilage or preferably chondroitin sulphate. A preferred neovascular regulator is chondroitin sulphate which also promotes or stimulates collagen synthesis and vascular tissue regeneration.

[0016] The multi-component compositions of this invention and treatment methods using them are based, at least in part, on a recognition that the conditions and symptoms associated with macroangiopathy and microangiopathy, are the result of a multi-factor etiology requiring consideration of multiple biochemical factors to successfully ameliorate or reverse these conditions or symptoms.

[0017] In more preferred compositions, the antioxidant, neovascular regulator, collagen synthesis factors, and nutrient components are combined with components that regulate glucose or insulin levels, regulate lipids, regulate cholesterol absorption, facilitate or enhance reconstruction of the vascular matrix and/or suppress inappropriate immune response.

[0018] In more preferred embodiments, the compositions of this invention employ different components having the same or similar biochemical or therapeutic functionality. These functionally similar components may differ in source (e.g., extracts of different plants), differ in chemical structure and/or different effective half-life on administration. Such combinations of different components with similar activities provide synergistic nonadditive benefits and improvements. Components of the compositions of this invention may themselves be multi-component mixtures with each subcomponent having differing functionality. Different composition components may have more than one biological function in the mixture and different components may have distinct, yet overlapping, biological functions. The use of functionally similar components which are structurally distinct or derived from different sources allows the inclusion of sufficiently high levels of total material to achieve a desired level of activity while avoiding the potential toxic effect that may result from use of high levels of any single component. The use of a combination of functionally similar components in a therapeutic/nutritional composition provides therapeutical active species having different half-lives. For example, preferred compositions of this invention combine two or more different antioxidants or components having antioxidant effect.

[0019] I. Specific Formulas for use in the Treatment and Prevention of Diabetic Complications Associated with Microangiopathy, such as Nephropathy and Retinopathy, Include:

[0020] 1. Formula IA which comprises:

[0021] (i) A plant extract having antioxidant effect comprising bioflavanoids, particularly an extract providing a major source of proanthocyanidins, such as Bilberry extract, grape seed extract, or pine bark extract. Bioflavanoids of lower proanthocyanidin content, for example, ginkgo biloba, can also be used to supplement major sources; combinations of plant materials and extracts can also be employed;

[0022] (ii) Tea polyphenols providing for increased glucose tolerance and additional antioxidant benefit;

[0023] (iii) Absorbable zinc, preferably zinc(Krebs) to supplement dietary deficiency or loss due to diabetic excretion; and

[0024] (iv) A neovascular regulator selected from genistein and/or daidzein; soy isolate comprising genistein and/or daidzein; cartilage or chondroitin sulphate; chondroitin sulphate is a preferred neovascular regulator also associated with collagen synthesis; shark cartilage is a preferred cartilage preparation.

[0025] 2. Formula IB which comprises:

[0026] Vitamin C;

[0027] Vitamin E;

[0028] Bilberry Extract (preferably low OPCs, e.g., 25% oligomers OPCs);

[0029] Pine Bark Extract (preferably high OPCs, e.g., 85% or greater OPCs);

[0030] Tea polypbenols;

[0031] Absorbable zinc, particularly zinc(Krebs);

[0032] Chondroitin sulphate; and

[0033] Soy isolate, or equivalent levels of genistein and/or daidzein; and optionally a cartilage preparation.

[0034] (OPCs are oligomeric proanthocyanidins)

[0035] 3. Formula IC wbich comprises:

[0036] Formula IB; and

[0037] Glucosamine sulpbate (a preferred glycosaminoglycan and source of glycosamine, a building block for collagen syntbesis);

[0038] 4. Formula ID which comprises:

[0039] Formula IC; and

[0040] Antioxidant carotenoids, such as lutien and/or zeaxanthin; and

[0041] Vitamin D3, preferably derivatives thereof wbich induce little or substantially no hypercalcification (e.g., 22-oxa-Vitamin D3).

[0042] 5. Formula IE which comprises:

[0043] Formula ID;

[0044] Grape Seed Extract (also known as leucoanthocyanidin);

[0045] Vitamin A(acetate or palmitate);

[0046] A source of taurine, particularly homotaurine;

[0047] Absorbable magnesium, particularly magnesium (Krebs);

[0048] Absorbable calcium, particularly calcium (Krebs);

[0049] Absorbable cbromium, particularly chromium picolinate; and

[0050] Absorbable potassium, particularly potassium citrate.

[0051] 6. Formula IF whicb comprises:

[0052] Formula IE;

[0053] A source of essential fatty acids, particularly conjugated dienoic fatty acids; for example, linoleic acid

[0054] Folic acid;

[0055] Vitamin B2;

[0056] Vitamin B6; and

[0057] Vitamin B12.

[0058] 7. Formula IG which comprises:

[0059] Formula IF; and

[0060] Melatonin.

[0061] 8. Formula IH which comprises:

[0062] Formula IG;

[0063] Gymnema sylvestre;

[0064] Fenugreek Seed (preferably defatted powder);

[0065] A source of omega-3 fatty acids, particularly conjugated dicnoic fatty acids, e.g., linolcic acid (ALA) and/or enosapentaenoic acid (EPA), a preferred source is ground flax seed;

[0066] Ginkgo biloba; and

[0067] Lycopene and/or beta-carotene (additional antioxidant carotenoids).

[0068] 9. Formula IJ which comprises

[0069] Formula IH;

[0070] L-carnitine;

[0071] Quercitin;

[0072] Coenzyme Q, particularly Coenzyme Q_{10}(CoQ_{10});

[0073] N-acetyl-L-cysteine; and

[0074] Thioctic acid (alpha lipoic acid).

[0075] 10. Formula IK which comprises:

[0076] Formula IJ;

[0077] Absorbable selenium;

[0078] Indole-3-carbinol;

[0079] Glutathione;

[0080] Amino acids selected from: L-alanine, L-cysteine, or L-tryptophan;

[0081] Branched chain amino acids: L-leucine, L-isoleucine or L-valine;

[0082] Betaine hydrochloride;

[0083] pepsin; and

[0084] Sodium bicarbonate.

[0085] 11. Formula IL which comprises:

[0086] Formula IK:

[0087] Eugenol; and

[0088] Pytosterols, particularly C24-substituted cholesterol derivatives xFormulas IA-IL are optionally combined with aspirin and NSAIDS (non-steroid anti-inflanmatories) and may optionally be combined with protamine sulphate and/or DHEA (dehydroepiandrosterone). Formulas IA-IK can be combined with the peptide hormones: calcitonin and /or amylin, which provide positive therapeutic benefit for individuals with diabetes. Red Wine Extract, a powerful proanthocyanidin-containing extract can also be employed in the Formulas IA-IL in place of, or in addition to, other proanthocyanidin

[0089] II. Specific Formulas for use in Wound Healing, Particularly Healing of Chronic, Persistent or Recurring Wounds including Decubitus Ulcers Include:

[0090] 1. Formula IIA [Non-diabetic formula] which comprises:

[0091] (i) A plant extract having antioxidant effect comprising a major source of bioflavonoids, such as proanthocyanidins, including Bilberry extract, Grape seed extract or Pine Bark extract. Pine Bark extract is preferred. Pine Bark Extract is a superior antioxidant and anti-inflammatory which also promotes collagen synthesis and inhibits mammalian collagenases. Bioflavanoids of lower proanthocyanidin content, e.g., Ginkgo Biloba can also be used to supplement major sources; combinations of plant materials and extracts can also be employed;

[0092] (ii) A neovascular regulator particularly chondroitin sulphate which promotes rebuilding of collagenous tissue and enhances glucosamine performance;

[0093] (iii) Glucosamine sulphate and other sources of glucosamine which increase hyaluronic acid production and promote wound healing; and

[0094] (iv) A source of absorbable magnesium, preferably magnesium malate to support collagen synthesis and glucosamine utilization.

[0095] 2. Formula IIB [Non-diabetic formula] which comprises

[0096] Pine bark extract;

[0097] Grape seed extract (leucoanthocyanidin);

[0098] Tea polyphenols;

[0099] Chondroitin sulphate;

[0100] Glucosamine sulphate;

[0101] Vitamin C (antioxidant which promotes collagen formation and strengthens capillaries);

[0102] Absorbable magnesium; and

[0103] Amino acids selected from: L-arginine, L-cysteine, glycine, L-methionine, L-threonine or L-proline

[0104] 3. Formula IIC [Non-diabetic formula] which comprises

[0105] Formula IIB;

[0106] Thioctic acid (alpha-lipoic acid);

[0107] Bilberry extract;

[0108] Nicotinamide;

[0109] Aloe vera (preferably in powdered form);

[0110] Absorbable calcium, e.g., calcium citrate, calcium malate and mixtures thereof;

[0111] Vitamin A (antioxidant which increases collagen content of tissue);

[0112] Absorbable zinc, e.g., zinc (Krebs); and optionally

[0113] A cartilage preparation, particularly bovine cartilage.

[0114] 4. Formula IID [Non-diabetic formula] which comprises:

[0115] Formula IIC;

[0116] A source of essential fatty acids, in particular, conjugated dienoic fatty acid, i.e., linoleic acid;

[0117] Folic acid;

[0118] Vitamin B12;

[0119] Vitamin B6;

[0120] Co-Q-10;

[0121] Vitamin D3 (derivatives having minimal hypercalcification);

[0122] Absorbable potassium, e.g., potassium citrate;

[0123] Vitamin K1; and

[0124] A source of taurine (L-taurine or homo-taurine).

[0125] 5. Formula IIE [Non-diabetic formula] which comprises:

[0126] Formula IID;

[0127] Vitamin B2;

[0128] Vitamin B1;

[0129] Betaine hydrochloride;

[0130] Pepsin;

[0131] Sodium bicarbonate;

[0132] Ginkgo biloba;

[0133] Antioxidant carotenoids (Lutein or zeaxanthin or beta-carotene and/or lycopene); and

[0134] Vitamin B5 (pantothenic acid).

[0135] 6. Formula IIF [Non-diabetic formula] which comprises:

[0136] Formula IIE;

[0137] N-acetyl-L-cysteine;

[0138] Protamine sulphate;

[0139] Soy isolate; and optionally,

[0140] Phytosterols, particularly C24 substituted cholesterol derivatives (e.g., Cholestatin III); and/or

[0141] Mineral complex (preferably without iron) including nutritional minerals not yet included in the formula.

[0142] 7. Formula IIG [Non-diabetic formula] which comprises:

[0143] Formula IIF;

[0144] Vitamin B complex components (those not already in Formula IIF); and

[0145] A cartilage preparation, preferably bovine cartilage.

[0146] 8. Any of Formulas IIA-IIG can be prepared as a diabetic formulation by including any of the following not already included:

[0147] Gymnema sylvestre;

[0148] Fenugreek seed;

[0149] Amylin;

[0150] Glutathione;

[0151] Thiotic acid;

[0152] Absorbable chromium, e.g., chromium picolinate; and

[0153] By deleting nicotinamide, if present.

[0154] 9. Excess iron can be inhibitory to wound healing. Iron is thus excluded from the mineral complex of Formula IIF. Any of Formulas IIA-IIG, both the non-diabetic and diabetic formulations, can be prepared for use with iron-deficient individuals by addition of:

[0155] Absorbable iron sufficient to satisfy deficiency.

[0156] 10. Omega-3-fatty acids are excluded from the wound healing compositions above as potentially inhibitory in the earlier stages of wound healing. These components can, however, be included in a preventative wound healing formula, before wounds occur such as when beginning a long hospital stay or after wound sites are sufficiently healed.

[0157] Formulas IIA-IIG, both non-diabetic and diabetic formulations, are intended for oral administration.

[0158] Any of the Formulas IIA-IIG (diabetic and non-diabetic) can be formulated as a wound healing ointment by addition of the following ingredients to the oral wound healing formulation:

[0159] (i) An antibiotic;

[0160] (ii) Honey (preferably raw) and/or sugar and/or glycerine;

[0161] (iii) An alginate (a gelling polysaccharide, preferably from seaweed, e.g., sodium or calcium alginate)

[0162] (iv) One or more amino acids selected from the group L-proline; L-cysteine; L-arginine; Glycine; L-threonine; or Branched chain amino acids (if not already included in oral formulation).

[0163] Any antibiotic appropriate for topical application can be employed including, for example, hydrogen peroxide (30%), polyethylene glycol 400, acetic acid, or betadine. Sugars can include brown sugar, caster sugar or powdered sugar. Wound healing ointments optionally include cartilage, allantoin and/or urea for additional wound healing benefit. Antibiotics and other active ingredients are included in wound healing ointment in an amount effective for providing the desired therapeutic or nutrient effect (e.g., to compensate for a local deficiency). Sugars, honey or glycerine can be replaced with a pharmaceutical carrier appropriate for ointment formulation. In preferred embodiments, sugars and honey (or pharmaceutical carrier) represent about 50% to about 70% (be weight); antibiotics represent 20-40% (by weight); and other ingredients represent about 1-20% (by weight) of the ointment.

[0164] Wound healing ointments can also contain pH control agents, vitamins and/or mineral combination, additional vascular enhancers, osmotic stabilizers, and enzymes.

[0165] Excipients for topical application include among others: alginate, pectin, gelatin, gelatin derivatives, cellulose derivatives, quar gum, acacia gum, karaya gum, tragacanth gum, locust bean gum, agar, dextran, derivatives of dextran, ghatti gum, xanthan gum, polyvinylpyrolidone, polyethylene, polyethylene glycol, glycerol, polypropylene glycol.

[0166] Other additives that may be combined with ointments and other topical formulas include coloring agents, flavoring agents, thickeners, emulsifying agents, surfactants, and solubilizing agents.

[0167] Formulas IIA-IIH are optionally combined with aspirin and or NSAIDS where appropriate. Red Wine Extract, a powerful proanthocyanidin-containing extract can also be employed in the Formulas IIA-IIH in place of, or in addition to, other proanthocyanidin.

[0168] Formulas IIA-IIH (diabetic and non-diabetic) can optionally include:

[0169] Dragon's Blood (a proanthocyanidin containing extract with particular wound healing function); and/or

[0170] *Centella asiatica* or its extract.

[0171] III. Specific Formulas for use in the Treatment and Prevention of Neuropathy Include:

[0172] 1. Formula IIIA [Non-diabetic] which comprises:

[0173] (i) A plant extract having antioxidant effect comprising a major source of proanthocyanidins, such as Bilberry extract, grape seed extract or pine bark extract. Bioflavanoids of lower proanthocyanidin content, e.g., ginkgo biloba can also be used to supplement major sources; combinations of plant materials and extracts can also be employed;

[0174] (ii) A neovascular regulator, particularly chondroitin sulphate; and

[0175] (iii) Glucosamine sulphate (a source of glucosamine).

[0176] 2. Formula IIIB [Non-diabetic] which comprises:

[0177] Pine Bark extract;

[0178] Chondroitin sulphate;

[0179] Glucosamine sulphate;

[0180] Absorbable magnesium, e.g., magnesium malate;

[0181] Absorbable calcium, e.g., calcium (Krebs);

[0182] Thioctic acid (alpha-lipoic acid);

[0183] Ginkgo biloba;

[0184] Tea polyphenols;

[0185] Vitamin C; and

[0186] A source of essential fatty acids. (Vitamin C and essential fatty acid may both be supplied as ascorbyl-gamma-linoleic acid, for example.

[0187] 3. Formula IIIC [Non-diabetic] which comprises:

[0188] Formula IIB;

[0189] Vitamin B complex;

[0190] Co-Q-10;

[0191] Vitamin E;

[0192] Vitamin D3, preferably a derivative inducing little or substantially no hypercalcification;

[0193] Vitamin K; and

[0194] A source of omega-3-fatty acids, e.g., flax seed.

[0195] 4. Formula IIID [Non-diabetic] which comprises:

[0196] Formula ITIC;

[0197] Absorbable potassium, e.g., potassium citrate;

[0198] Absorbable zinc, e.g., zinc (Krebs);

[0199] Soy isolate;

[0200] Antioxidant carotenoids (e.g., lutien or zeaxanthin or beta carotene and/or lycopene); and

[0201] Folic acid.

[0202] 5. Formula IIIE [Non-diabetic] which comprises:

[0203] Formula IIID;

[0204] Grape seed extract (leucoanthocyanidin);

[0205] Vitamin A;

[0206] A source of taurine (e.g., homotaurine or L-taurine); and

[0207] Protamine sulphate.

[0208] 6. Formula IIIE [Non-diabetic] which comprises:

[0209] Formula IIID; and/or

[0210] Branched-chain amino acids; and/or Melatonin; and/or

[0211] A source of cartilage or a cartilage preparation, e.g., shark cartilage.

[0212] 7. Formula IIIF [Non-diabetic] which comprises:

[0213] Formula IIID±options of Formula IIIE;

[0214] Absorbable selenium;

[0215] N-acetyl-L-cysteine;

[0216] Glutathione;

[0217] Betaine hydrochloride;

[0218] Pepsin;

[0219] Sodium bicarbonate;

[0220] Bilberry extract; and optionally Phytosterols; and/or

[0221] Mineral complex (except for the minerals noted above in Formula IIIA-E).

[0222] 8. Formulas IIIA-IIIF can be prepared as a diabetic formulation by addition of any of the following not already included:

[0223] Gymnema sylvestre;

[0224] Fenugreek seed;

[0225] Glutathione;

[0226] Thioctic acid (alpha-lipoic acid, if not already included in formula);

[0227] Absorbable chromium, as chromium picolinate; and optionally, Myo-inositol and biotin.

[0228] Formulas IIIA-IIIF for treatment and prevention of neuropathy (diabetic and non-diabetic) can be combined with aspirin and/or NSAIDS.

[0229] Formulas IIIA-IIIF (diabetic and non-diabetic) can also include glutathione peroxidase which has additional antioxidant effect. Red Wine Extract, a powerful proanthocyanidin-containing extract can also be employed in the Formulas IIIA-IIIF in place of, or in addition to, other proanthocyanidins.

[0230] Components of Formulas IIIA-IIIF (diabetic and non-diabetic) can be formulated in appropriate carrier materials for topical application to affected areas.

[0231] IV. Specific Formulas for use in the Prevention and Treatment of Cardiovascular Disease Include:

[0232] 1. Formula IVA [Non-diabetic] which comprises:

[0233] (i) A plant extract having antioxidant effect comprising bioflavanoids, particularly an extract providing a major source of proanthocyanidins, such as Bilberry Extract, Grape Seed Extract, or Pine Bark Extract. Bioflavanoids of lower proanthocyanidin content, for example, Ginkgo Biloba, can also be used to supplement major sources; combinations of plant materials and extracts can also be employed;

[0234] (ii) Absorbable zinc, preferably zinc(Krebs) to supplement dietary deficiency or loss due to diabetic excretion; and

[0235] (iii) A neovascular regulator selected from genistein and/or diadzein; soy isolate comprising genistein and/or diadzein; shark cartilage or chondroitin sulphate.

[0236] 2. Formula IVB [Non-diabetic] which comprises:

[0237] Vitamin C;

[0238] Vitamin E;

[0239] Bilberry Extract (preferably low OPCs, e.g., 25% oligomers OPCs);

[0240] Pine Bark Extract (preferably high OPCs, e.g., 85% or greater OPCs);

[0241] Tea polyphenols;

[0242] Absorbable zinc, particularly zinc(Krebs);

[0243] Soy isolate, or equivalent levels of genistein and/or diadzein; and

[0244] Chondroitin sulphate;

[0245] Glucosamine sulphate; and optionally a cartilage preparation, e.g., shark cartilage

[0246] (OPCs are oligomeric proanthocyanidines)

[0247] 3. Formula IVC [Non-diabetic] which comprises:

[0248] Formula IVB;

[0249] Antioxidant carotinoids, such as lutein and/or zeaxanthin;

[0250] Grape Seed Extract (also known as leucoanthocyanidin);

[0251] Vitamin A (acetate of palmitate);

[0252] A source of taurine, particularly homotaurine;

[0253] Protamine sulphate;

[0254] Absorbable magnesium, particularly malate and/or magnesium (Krebs);

[0255] Absorbable calcium, particularly calcium (Krebs);

[0256] Absorbable potassium;

[0257] Vitamin K1, an anti-atherosclerotic and antioxidant: and

[0258] Vitamin D3, preferably derivatives thereof which induce little or substantially no hypercalcification (e.g., 22-oxa-Vitamin D3).

[0259] 4. Formula IVD which comprises:

[0260] Formula IVC

[0261] A source of essential fatty acids, e.g., conjugated dienoic fatty acids, such as linoleic acid;

[0262] Melatonin;

[0263] Folic acid;

[0264] Vitamin B2;

[0265] Vitamin B6;

[0266] Vitamin B12

[0267] Antioxidant carotenoids, including lycopene and/or beta carotene; and

[0268] A source of omega-3-fatty acids, e.g., flax seed.

[0269] 5. Formula IVE [Non-diabetic] which comprises:

[0270] Formula IVD;

[0271] Ginkgo Biloba; and

[0272] Quercitin (or other antioxidant bioflavonoid)

[0273] 6. Formula IVF [Non-diabetic] which comprises:

[0274] Formula IVE;

[0275] Coenzyme Q, particularly Coenzyme Q_{10} (CoQ10);

[0276] N-acetyl-L-cysteine;

[0277] Glutathione;

[0278] Thioctic acid (alpha lipoic acid);

[0279] Absorbable selenium (an organoselenium compound, such as selenomethionine);

[0280] Indole-3-carbinol;

[0281] Glutathione;

[0282] Betaine hydrochloride;

[0283] Pepsin;

[0284] Sodium bicarbonate;

[0285] Nicotinamide;

[0286] Amino acids selected from: L-arginine, glycine, L-methionine, L-tyrosine, L-tryptophan, or gamma-amino butyric acid; and

[0287] Phytosterols, particularly C-24-substituted cholesterol.

[0288] 7. Formulas IVA-IVF can be prepared as a diabetic formulation by addition of any of the following not already included:

[0289] Gymnema sylvestre;

[0290] Fenugreek seed;

[0291] Glutathione;

[0292] Thioctic acid;

[0293] Absorbable chromium, e.g., chromium picolinate; and by deletion of nicotinamide, if present.

[0294] The compositions. of formulas IVA-IVF (diabetic and non-diabetic) can be combined with aspirin and/or NSAIDS. Red Wine Extract, a powerful proanthocyanidin-containing extract can also be employed in the Formulas IVA-IVF in place of, or in addition to, other proanthocyanidin

[0295] V. Specific Formulas for use in the Prevention and Treatment of Dental Carics and Periodontal Disease Include:

[0296] 1. Formula VA [Non-diabetic] which comprises:

[0297] (i) A plant extract having antioxidant effect comprising a major source of proanthocyanidins, such as Bilberry Extract, Grape Seed Extract, or Pine Bark Extract. Bioflavanoids of lower proanthocyanidin content, for example, Ginkgo biloba, can also be used to supplement major sources; combinations of plant materials and extracts can also be employed;

[0298] (ii) Absorbable calcium, such as calcium citrate, calcium malate or mixtures thereof; and

[0299] (iii) A source of Vitamin D3, preferably a Vitamin D3 derivative or analog that induces little or substantially no hypercalcification.

[0300] 2. Formula VB [Non-diabetic] which comprises:

[0301] Pine bark extract;

[0302] Tea polyphenols;

[0303] Absorbable calcium, preferably calcium citrate/malate; and

[0304] Vitamin D3, preferably derivatives thereof which induce little or substantially no hypercalcification (e.g., 22-oxa-Vitamin D3).

[0305] 3. Formula VC [Non-diabetic] which comprises:

[0306] Formula VB;

[0307] Absorbable magnesium, particularly magnesium malate;

[0308] Absorbable strontium;

[0309] L-lysine;

[0310] Absorbable zinc, e.g., zinc (Krebs); and

[0311] N-acetyl-L-cysteine.

[0312] 4. Formula VD [Non-diabetic] which comprises:

[0313] Formula VC;

[0314] Cysteine;

[0315] Absorbable silicon (as a silicate, e.g., as a trisillicate salt);

[0316] Chondroitin sulphate;

[0317] Glucosamine sulphate;

[0318] Quercitin (or other antioxidant bioflavonoid);

[0319] Absorbable potassium; and

[0320] Vitamin C.

[0321] 5. Formula VE [Non-diabetic] which comprises:

[0322] Formula VD;

[0323] Absorbable manganese, particularly manganese aspartate;

[0324] Soy isolate;

[0325] Vitamin K1 (a regulator of calcium metabolism);

[0326] Vitamin A;

[0327] Thioctic acid (alpha lipoic acid);

[0328] Co-Q-10; and optionally

[0329] A cartilage preparation, preferably bovine cartilage.

[0330] 6. Formula VF [Non-diabetic] which comprises:

[0331] Formula VE;

[0332] Absorbable cadmium;

[0333] Betaine hydrochloride;

[0334] Pepsin; and

[0335] Sodium bicarbonate.

[0336] 7. Formula VG [Non-diabetic] which comprises:

[0337] Formula VF;

[0338] Vitamin E;

[0339] Omega-3-fatty acid source, e.g., flax seed;

[0340] Grape seed extract (leucoanthocyanidin);

[0341] Bilberry extract; and optionally sulphated saccharides (e.g., sucraflate);

[0342] 8. Formula VH [Non-diabetic] which comprises:

[0343] Formula VG;

[0344] L-taurine;

[0345] Folic acid;

[0346] Glutathione;

[0347] A source of essential fatty acid;

[0348] Ginkgo biloba;

[0349] Protamine sulphate;

[0350] Vitamin B complex; and optionally

[0351] Plant sterols.

[0352] 9. Formulas VA-VH can be prepared as a diabetic formulation by addition of any of the following not already included:

[0353] Gymnema sylvestre;

[0354] Fenugreek Seed;

[0355] Glutathione;

[0356] Thioctic acid; and

[0357] Absorbable chromium (e.g., chromium picolinate).

[0358] Compositions of Formulas VA-VH (diabetic and non-diabetic can be combined with aspirin and/or NSAIDS, if appropriate. Red Wine Extract, a powerful proanthocyanidin-containing extract can also be employed in the Formulas VA-VH in asplace of, or in addition to, other proanthocyanidin.

[0359] The components listed in all formulas above, are believed to have the biological nutrient or therapeutic functions as listed above and as indicated in Tables 1 and 2, where a single component may provide multiple functions.

[0360] Compositions of the present invention also include those in which the primary compositions, Formulas IA-VA, are combined with any of the additional ingredients of other specific formulas IB-IK, IIB-IIG, IIIB-IIIF, IVB-IVF, VB-VH, respectively, of its type.

[0361] Formulas of this invention listed above can also be combined with garlic extract (allicin), licorice extract, ginger, red wine extract, citrus pectin and/or marine tunicates or their isolates each of which can function for neovascular regulation and may provide additional therapeutic or nutritive benefit. The formulas of this invention can optionally include nutrients, vitamins and minerals other than those specifically listed to supplement particular nutritional deficiencies of given individuals, for example, chromium, iron, or other mineral may be provided or its concentration increased to supplement a given deficiency. Similarly, a particular vitamin or amino acid deficiency can be supplemented. Analogously, a given formulation can be adapted for sensitivities or allergies of a given individual.

[0362] Components that enhance or facilitate desirable enzyme activity, e.g. lysyl oxidase (an enzyme which par-

ticipates in collagen synthesis); nitric oxide inhibitors, other antioxidant carotenoids or flavanoids, additional antihyperlipoproteinemics, including probucol and blood thinning agents, e.g. heparin can be combined with any of the formulas listed above.

[0363] Celluar antioxidants, such as the enzymes: superoxide dismutase and catalyze or thiols, including glutathione peroxidase, can be included in any of specific formulas listed above. L-carnitine (which may be in the form of L-acetyl carnitine or L-propionyl carnitine) can be combined with any of the specific formulas above.

[0364] Treatment using the compositions of this invention can be combined with hormone therapy and or hormone supplementation, including estrogenic hormone therapy or supplementation, thyroid hormone therapy or supplementation, treatment or supplementation with human growth hormone (HGH) and/or treatment or supplementation with DHEA (dehydroepiandrosterol).

[0365] The formulas of this invention can also be combined with appropriate growth factors, growth factor inhibitors and growth factor binding agents including, among others, fibroblast, epidermal, interleuken transforming and platelet-derived growth factors, agents that bind hyaluronic acid and/or collagen. The formulas of this invention can also be combined with immune suppression of T-lymphocytes.

[0366] The formulas of this invention can also be employed in combination with therapeutic methods shown to have beneficial effect for the disorders, conditions and diseases discussed herein. For example, wound healing formulas (oral and topical) can be used in combination with oxygenation therapy for improved wound healing benefit.

[0367] Other optional components of the formulas of this invention include antioxidants and/or preservatives, such as BHT (Butylated hydroxytoluene), BHA (Butylated hydroxyanisole), ethoxiquin and diphenyl phenylenediamine.

[0368] In general the amount of each component employed in the different compositions of this invention is sufficient to provide the desired therapeutic effect(s) or nutritive effect(s), as listed in Tables 1 and 2 and discussed herein, to an individual and avoid toxicity with continuing regular dosing. Because compositions of this invention can have multiple components with similar functionality, the effective amount of any given component needed to provide a given level of function in a given composition will depend on the quantities of other functionally similar components to be included in the composition.

[0369] Table 3 provides a list of preferred components for the compositions of this invention providing a preferred range of amounts of individual components that can be combined in the formulas of this invention. The amounts listed in Table 3 are average daily adult dosages.

[0370] Table 4 provides a list of preferred components for a therapeutic and preventative composition for diabetic complications, e.g., retinopathy and nephropathy of this invention. The table provides a preferred range of amounts of individual components that are combined in the formulas of this invention. The amounts listed in Table 4 are average daily adult dosages. In Table 4, two preferred diabetic complications formulas are provide. Formula B has somewhat higher levels of folic acid, riboflavin and pyridoxine compared to formula A. (Formula B employs the palmitate form of Vitamin A, while formula A employs Vitamin A acetate.) The specific compositions (A and B) of Table 4 are intended as an initial treatment dose. Lower daily dosage compositions can be employed after initial treatment to maintain beneficial effects. Alternatively, lower daily dosage compositions can be employed to forestall or prevent diabetes-related conditions in those at risk for developing them. Preventative and maintenance compositions may contain ingredients in addition to those listed in Table 1. Variation of the amounts of individual components in the preferred composition by up to about +/−20% will not significantly affect nutritive or therapeutic value. A broad range of effective amounts for each preferred component is provided in Table 3.

[0371] The primary formulas of this invention useful for treatment of symptoms and conditions associated with microangiopathy and macroangiopathy comprise components that (1) have antioxidant function to control oxidative stress, (2) are neovascular regulators which control angiogenesis, (3) promote and/or stimulate collagen synthesis and (4) optionally stabilize glucose and/or amylase factors; or (5) optionally supplement dietary deficiencies and counteract non-utilization or spillage by diabetics. Table 1 provides a summary of the biochemical functions of components that are useful in combination with the components of those primary formulas. A single component may provide more than one of the listed biological functions in a given composition.

[0372] One or more of the functionalities listed in Table 1 can be provided in the compositions of this invention by art-known drug equivalents. For example, art-known antidiabetic agents, antihypertensives, angiotensin converting enzyme inhibitors, vasodilators, anticholesteremics, antihyperlipoproteinemics, angiogenesis regulators, and enzyme co-factors can be combined in effective amounts for ameliorating symptoms and conditions associated with microangiopathy, particularly retinopathy and nephropathy, with formulas of this invention.

[0373] Compositions of this invention can be provided in a variety of nutrient and dosage forms including pills, tablets, capsules, lozenges, powders, solutions, suspensions, injection dosage forms and the like. Compositions of this invention can be administered to individuals orally, intravenously, and by various forms of injection and various forms of absorption (e.g., sublingual). Active ingredients of the formulas of this invention can be combined with excipients, fillers, buffering agents and the like to prepare desired dosage forms. Generally preferred dosage forms are those appropriate for oral administration. Wound healing compositions and compositions for treatment of neuropathy are provided for topical application.

[0374] This invention also encompasses methods of treatment to ameliorate the symptoms and disease conditions associated with microangiopathy and macroangiopathy which comprise administration of the compositions of this invention to an individual suffering from symptoms or conditions resulting these disorders. More specifically, the invention provides methods for ameliorating diabetic retinopathy and nephropathy. Methods of this invention can be combined with other compatible known methods for treat-

ment of diabetic complications. The compositions of this invention for treatment of diabetic complications are best applied in a treatment regime that emphasizes good diabetes control. Methods of this invention can also ameliorate ocular conditions including macular degeneration, glaucoma and cataracts.

DETAILED DESCRIPTION OF THE INVENTION

[0375] The nutrient and therapeutic compositions of this invention are generally directed toward the improvement of disease conditions and symptoms that are associated with vascular and capillary degeneration: macroangiopathy and microangiopathy. Compositions of this invention also provide for prevention or retardation of the development or worsening of certain disease conditions or symptoms associated with vascular and capillary degeneration in individuals at risk for developing these disorders, for example, in individuals with diabetes or individuals exhibiting symptoms of cardiovascular disease. This invention provides formulas for treatment and prevention of diabetic complications including retinopathy, neuropathy and nephropathy. Formulas of this invention are also useful in the treatment and prevention of non-diabetic retinopathy, neuropathy and nephropathy. Formulas of this invention are also useful in the prevention and treatment of the symptoms and disease conditions of cardiovascular disease. Formulas of this invention are useful in wound treatment and are particularly useful in treating recurrent or slow-to-heal wounds including those that are a complication of diabetes. Formulas of this invention are also useful in the prevention and treatment of dental and periodontal disease conditions.

[0376] The formulas of this invention that are useful in the treatment and prevention of the various disease conditions discussed above combine a number of related ingredients. The therapeutic and preventative compositions of this invention are based at least in part on the inventor's recognition of similarities in etiology of the various disease conditions discussed above. In particular, the inventor considers that these conditions and disorders are, at least in part, caused by or exacerbated by oxidative stress and tissue destruction associated with oxidative damage. Further, the inventor considers that the disorders discussed above are, at least in part, caused by or exacerbated by microangiopathy and/or macroangiopathy, i.e., vascular and capillary degeneration. Vascular and capillary degeneration is, at least in part, caused by antioxidant stress. Further, the inventor considers that in each of the disease conditions and symptoms, for which formulas are provided herein, that stimulating and or promoting collagen synthesis is an important factor in prevention and treatment. In this regard, the various disease conditions discussed herein also relate in part aberrant tissue growth, for example due to lack of proper growth factors or lack of growth factor inhibitors. Furthermore, conditions associated with microangiopathy also suffer from the effects of deprivation of adequate nutrient, vitamin, cofactor and mineral supplies and particularly from inadequate supplies of nutrients, cofactors and the building blocks needed for restoration of the collagen matrix which is necessary for regeneration and healing of vascular tissue and tissue in general.

[0377] Diabetic complications of retinopathy and nephropathy are clearly associated with microangiopathy, improperly controlled vascularization and concomitant weakening of capillaries. The formulas of this invention for treatment of diabetic complications include antioxidants, neovascular regulators (particularly angiogenesis regulators) and factors that promote or stimulate collagen synthesis and restoration of the collagen matrix.

[0378] Cardiovascular disease is directly linked to vascular degeneration. Tissue damage induced, at least in part, by oxidative stress provides sites for lesion formation and plaque accumulation. Formulas of this invention for use in treatment and prevention of cardiovascular disease include antioxidants to prevent or limit oxidative tissue damage, growth factors (neovascular regulators) that stimulate repair of vascular tissue, factors that stimulate or promote collagen synthesis and other components of benefit for cardiovascular disease. The cardiovascular compositions of this invention can be formulated to include ingredients that are beneficial for diabetics.

[0379] The wound healing compositions of this invention are based on the premise that wounds that resist healing part from infection, result, at least in part, from microangiopathy. As noted above, microganiopathy is believed to involve oxidative stress, deficient neovascular regulation and deficient collagen synthesis. Microangiopathy is believed to promote nutrient and oxygen deprivation, and ineffective immune response at the wound site. All of these factors: oxidative stress, deficient neovascular regulation, deficient collagen synthesis, nutrient and oxygen deprivation and local immune deficiency are believed to contribute and/or exacerbate the slow healing process. All of these factors would contribute to destruction of cells and tissue faster than they can be replaced, leading to wounds that do not heal or that worsen.

[0380] The wound healing compositions of this invention concurrently attenuate these factors by (1) controlling oxidative stress and providing protection from free-radicals and other biological oxidation agents, (2) providing neovascular regulators, particularly inhibitors of angiogenesis, and/or collagen factors which promote or stimulate collagen synthesis and/or inhibitors of mammalian collagenases to enhance capillary and tissue repair, and (3) compensating for inadequate nutrient delivery by supplying minerals, vitamins and amino acids. The wounding healing compositions of this invention also provide for immune inflammation. The wounding healing compositions of this invention can be formulated to include ingredients that are beneficial for diabetics.

[0381] The compositions of this invention for treatment of neuropathy are based on the premise that neuropathy results, at least in part, from microangiopathy. As noted above, microangiopathy is believed to involve oxidative stress, immune inflammation, deficient neovascular regulation and deficient collagen synthesis. Oxidative stress, deficient neovascular regulation, deficient collagen synthesis, nutrient and oxygen deprivation and local immune deficiency are believed to contribute and/or exacerbate the slow healing process. All of these factors would contribute to destruction of cells and tissue faster than they can be replaced, leading to nerve tissue damage. In addition to providing for antioxidants, growth factors, factors that promote tissue growth and nutrient balance, formulas of this invention for neuropathy also provide additional vitamins, minerals and cofac-

tors linked to improvement in neuropathy. Neuropathy is a significant complication of diabetes. The neuropathy compositions of this invention can be formulated to include ingredients that are beneficial for diabetics.

[0382] The neuropathy compositions of this invention concurrently attenuate these factors by (1) controlling oxidative stress andimmune inflammation and providing protection from free-radicals and other biological oxidation agents, (2) providing neovascular regulators, particularly inhibitors of angiogenesis, and/or collagen factors which promote or stimulate collagen synthesis and/or inhibitors of mammalian collagenases to enhance capillary and tissue repair, and (3) compensating for inadequate nutrient delivery by supplying minerals, vitamins and amino acids. The neuropathy compositions of this invention can be formulated to include ingredients that are beneficial for diabetics.

[0383] The inventor has discovered that there is a significant improvement in periodontal disease and gingivitis in individuals who regularly take antioxidant supplements. Thus, oxidative stress is believed to be a factor in the development of such disease. It is believed that there is an indirect relationship between microangiopathy and dental and gum disease including periodontal disease. Gingivitis is associated with bacterial infection, however, the local environment and condition of the teeth, bone and gum tissue is believed to be important in development of dental and gum disease and infection. Tissue damage is believed to allow and exacerbate infection. Microangiopathy is also believed to also cause tissue damage resulting in nutrient and oxygen deficiency and exacerbation of tissue damage. Formulas of this invention for treatment and prevention of dental and gum disorders include antioxidants, factors that stimulate tissue repair and collagen synthesis and other nutrient and vitamin components that have benefit for the condition of the teeth and gums. Gum disease and tooth loss are complications of diabetes. The dental and periodontal compositions of this invention can be formulated to include ingredients that are beneficial for diabetics.

[0384] The treatment methods described herein employing the formulations of this invention are believed to derive unique and unexpected benefits from complementary and synergistic interactions between the various formula components acting together upon the various symptoms and conditions associated with the various diseases and disorders discussed herein. The success of these compositions in the treatments described is, at least in part, attributable to the multi-factor strategy employed to balance nutrient and metabolic deficiencies and to control oxidative stress, while promoting or stimulating vascular healing and/or collagen matrix repair, and inhibiting angiogenesis.

[0385] A description of various components (and their functional equivalents) of the formulas of the present invention follows:

[0386] Antioxidants

[0387] Antioxidants and antioxidant precursors are included in the compositions of this invention to combat oxidative stress and slow the deterioration of collagen tissues. In general, antioxidants are believed to protect vascular and capillary tissue to ameliorate macroangiopathy and microangiopathy. In the more preferred compositions of this invention a complementary antioxidant strategy is employed. Different chemical types of antioxidants are combined to provide enhanced antioxidant effect. Preferred antioxidant combinations include both hydrophilic (having affinity for water or polar groups) and hydrophobic (having an affinity for lipids) antioxidants and combinations of antioxidants from different natural plant sources. In a preferred embodiment, antioxidant vitamins (vitamins C or E), the mineral zinc and different plant bioflavonoid sources are combined to achieve complementary and synergistic antioxidant effects related to microvascular protection and healing associated with diabetic complications. In addition, antioxidant bioflavanoids, such as quercitin, and antioxidant carotenoids, such as lycopene, can be included for additional antioxidant effect.

[0388] Vitamin C or ascorbic acid can be provided in compositions of this invention in a variety of forms. Vitamin C is available from a variety of natural sources, which may also be employed in the compositions of this invention. Vitamin C is a hydrophilic antioxidant generally found in hydrophilic environments in the body, i.e., the bloodstream, the eye, interstitial spaces between cells and within cell membranes. It not only functions as a scavenger for singlet oxygen and hydroxy radicals, but it also replenishes spent Vitamin E by replacing electrons. In the bloodstream, Vitamin C reduces platelet aggregation, an anti-sclerotic effect. Vitamin C has a short half life and may interfere with diabetic glucose testing. For these reasons, it may be desirable, particularly in formulas for treatment of diabetic complications, to provide Vitamin C in smaller, more frequent doses or in a time released form. Forms of vitamin C suitable for use in the formulas of this invention include ascorbic acid, calcium and/or sodium ascorbate, and nicotinamide ascorbate.

[0389] Indole-3-carbinol is an antioxidant that provides functions similar to that provided by Vitamin C, however, is considered to provide protection against a broader range of biological oxidation agents.

[0390] Tocopherols (Vitamin E, d-alpha-tocopheryl salts) are hydrophobic, lipid-based compounds with antioxidant function. They are believed to have a primary role in protecting cell membranes from lipid peroxidation. Tocopherols also scavenge free radicals in the blood and help to protect Vitamin A and selenium. D-alpha tocopherol forms, the natural forms of Vitamin E, are preferred over the less bioactive d,1-tocopherol forms. Tocopherols can be provided in a variety of forms with different counterions. D-alpha-tocopheryl acetate and gamma-tocoperol are preferred for use in the compositions of this invention. Because some subjects can exhibit a slight rise in blood pressure when Vitamin E is first taken, smaller more frequent doses or a time-released form of Vitamin E may be more appropriate for microvascular protection in diabetics.

[0391] Lutien also called xanthophyll, a carotinoid related to beta-carotene, but not a pro-Vitamin A carotinoid, is itself a lipid peroxide scavenger and appears to promote the production of zeaxanthin, another abundant and powerful lipid-based antioxidant. Lutien is found in the human retina and is believed to act, possibly in a complementary manner with zinc, to protect retinal and macular tissue from oxidative damage. Lutien and zeaxanthin appear to perform the vast majority of the antioxidant function in the lens, retina and macula, of the eye with their highest concentrations

found in the macula. Lutien and zeaxanthin form the yellow pigment in the macula and central area of the retina which absorbs blue light and thereby appears to prevent photic damage to the macula. Lutein is reported to be deficient in the eyes of those having age-related macular degeneration. Zeaxanthin, an isomer of lutein, isolated from yellow corn grits, can be employed in compositions of this invention in place of or in additinn tn lutien.

[0392] Beta-carotene is an optional component of the compositions of this invention. It is a lipid-based, provitamin A antioxidant which quenches singlet oxygen and scavenges free radicals. It plays a role in protecting against lipid peroxidation and this function is especially valuable in the retina which contains high levels of poly-unsaturated fatty acids. Beta-carotene may also have a synergistic effect with other carotenoids, including lutein or zeaxanthin, for enhanced antioxidant function. In preferred antioxidant combinations, two or more carotinoid antioxidants are combined. Lycopene is another antioxidant flavanooid. Antioxidant flavanoids, including among others the flavanone glycosides quercitin, naringin, rutin and their aglucons, are superoxide scavengers and inhibit oxidation of LDL. In preferred antioxidant combinations, two or more antioxidant flavanoids are combined.

[0393] Alpha-lipoic acid (thioctic acid), which can be provided in the acid form or as an appropriate lipoate salt, e.g., sodium lipoate, is an antioxidant and free radical scavenger that reacts with reactive oxygen species including superoxide, hydroxyl radical, hypochlorous acid, peroxy radical, and singlet oxygen. Its reduced form, dihydrolipoate, is also an effective antioxidant. The d-form is the naturally-occurring optical isomer and preferred. The dl-form is available and can be employed in place of the d-form. Alpha-lipoic acid and its reduced dihydrolipoate form can bind to proteins including albumin which can prevent glycation reaction.

[0394] Creatine phosphate is reported to have an anti-ischemic effect and to function as an anti-oxidant. It may also function to protect myocardial tissue from damage due to free radiacals.

[0395] The mineral zinc, which is discussed in more detail below, is associated with protecting against lipid peroxidation in retinal tissue, possible due to its enhancement of superoxide dismutase function. The mineral potassium, also discussed below, inhibits superoxide anion.

[0396] Bioflavonoids containing proanthocyanidins scavenge free radicals and chelate some minerals to prevent them from oxidizing. Thesc bioflavonoids arc found in most plants from which they can be extracted. Commercially available proanthocyanidin-containing plant extracts include: grape seed extract (also called leucoanthocyanidin), pine bark extract (including "Pycnogenol" (Trademark, Horphag)), and Bilberry extract. Ginkgo Biloba and other plants can provide bioflavonoids of lower proanthocyanidin content which can also supplement antioxidant effect. These materials and extracts contain rather complex mixtures of catechins, tannins, oligomers and proanthocyanidins, at leasi some of which protect membranes from lipid peroxidation, and inhibit supernxides. They are hydrnphilic antioxidants, which are many times more effective than most antioxidant nutrients at controlling free radicals, superoxides and lipid peroxides. Individual plant materials which can provide proanthocyanidins may also provide other therapeutic benefits, for example, garlic and willow bark (a source of salicylic acid) may provide additional benefit.

[0397] Oligomcric proanthocyanidins (OPCs) arc polymcr chains of 10 or less catechins which yield red anthocyanidin when boiled in an aqueous solution of 10% hydrochloric acid. Proanthocyanidins do not contain condensed tannins but are composed of nearly 60% catechin forms which have an extremely high affinity for collagen. Catechin binds tightly to collagen, modifies its structure by crosslinking and causes it to be resistant to enzyme degradation, such as by collagenase, or by lipid peroxidation and superoxide radicals. Proanthocyanidins inhibit capillary resistance and capillary permeability and, thus, improve vascular damage and deterioration. Collagen accumulates in vessel walls in endothelia, the connective matrix, elastin and phospholipids which helps to maintain structural integrity and protect these structures from pcroxidc anion damagc. Plant extracts employed in this invention as sources for proanthocyanidins contain varying levels of OPCs. Antioxidant effectiveness of an extract generally increases with increasing levels of OPCs in the extract.

[0398] Dragon's Blood Croton spp. (Pieters, L., et al. (1995) *Phytomedicine* 1: 17-22) comprising antioxidant proanthocyanidines, has been associated with wound healing. This material can be optionally combined with wound healing compositions of this invention.

[0399] Red wine extract is a source of proanthocyanidins and tannins. Such extracts have anti-oxidant effect and may function to prevent platelet aggregation.

[0400] Catechins normally protect cell membranes from lipid peroxidation. Proanthocyanidins also help to deliver and bind Vitamin C to cell cites and can function to replace Vitamin C at times of ascorbic acid deprivation.

[0401] Compositions of this invention can contain one or more sources of proanthocyanidins which are included as antioxidants in the formula. Proanthocyanidins also promote vascular healing and integrity by restoring the collagen matrix. Different sources of proanthocyanidins, i.e., plant extracts, can also display other therapeutically beneficial functinns in compositions of this inventinn.

[0402] Bilberry extract is useful in the treatment of retinopathy. It may contain 5 types of anthocyanocides which account for most of its activity and 25% of its volume. While Bilberry extract inhibits superoxides and lipid peroxide to some degree, it is low in oligomeric proanthocyanidins (OPCs) and therefore is less effective at controlling these free radical forms than leucoanthocyanidin (grape seed extract, for example) described below. Bilberry has an unusual anti-inflammatnry effect, pnssibly because it can suppress leukotriene production. In addition, proanthocyanidins can achieve concentrations in tissue (kidney and skin) up to 5 times the level contained in the bloodstream. High tissue concentrations can remain up to 24 hours after serum concentrations have been depleted. These factors contribute to Bilberry's role in microvascular protection and repair and are particularly relevant to nephropathy, but also useful in treating other diabetic complications described herein.

[0403] The proanthocyanidin-cntaining extract of grape seeds includes the material called leucoanthocyanidin. This commercially available material is obtained from white

grape pips and is the most effective form of proanthocyanidin, yet discovered, for inhibiting superoxides and lipid peroxidation. This is believed to be due to the high level of oligomeric proanthocyanidins (OPCs) in the grape seed extract which strongly relates to vascular stabilization as described above. Red grape extract which is a good source of resveratrol can also be employed in this invention for antioxidant effect and other benefits.

[0404] Pine Bark Extract, some preparations of which are known by the trade name "Pycnogenol," is similar to leucoanthocyanidin, having relatively high OPC levels, but may possess better ability to suppress phagocytes.

[0405] Ginkgo biloba is a "middle range" proanthocyanidin possessing many of the functional characteristics of both Bilberry extract and grape seed extract, but these active components are apparently present in lower concentrations. Ginkgo biloba can cause dilation of arteries, capillaries and veins and inhibit platelet aggregation. Ginkgo biloba also functions to inhibit high blood pressure which is an important reason for its inclusion in compositions of this invention.

[0406] Green tea extract, tea polyphenols, contains a small amount of 2-3% of proanthocyanidin. It nevertheless is a potent antioxidant for lipid peroxides, superoxides and hydroxyl radicals. It contains relatively high concentrations of (−) epigallocatechin gallate (EGCg), a condensed tannin polyphenol. In addition to antioxidant function, tea polyphenols also have anti-platelet, anti-cholesterolemia, anti-hypertension, anti-hyperglycemic and anti-mutagenic activities. Tea polyphenols also assist theoflavin digallate in acting as an angiotensin converting enzyme inhibitor, but do not have the undesired pro-oxidant properties of captopril.

[0407] The five sources of bioflavonoids, Bilberry, grape seed extract (leucoanthocyanidin), Ginkgo biloba, pine bark extract ("Pycnogenol") and green tea extract (tea polyphenols) described above have significant complementary and synergistic chemical function that in combination with other ingredients and antioxidants in the formulas of this invention promote the microvascular benefits needed to improve retinopathy as well as other diabetic complications.

[0408] N-Acetyl-l-cysteine is a free radical scavenger and is very effective for lowering lipoprotein (a) [LP(a)] concentrations in vivo. IIigh levels of LP(a) are associated with increased risk to atherosclerosis and thrombic disease and are believed to accelerate microvascular disease in diabetes. Glutathione may also be employed in the formulations herein, as a free-radical scavenger.

[0409] Neovascular Regulators

[0410] Normal angiogenesis regulation appears to be accomplished by a variety of means. Endogenous factors, e.g., body chemistry, genetics, as well as exogenous factors, e.g., types of food consumed, appear to play a role in this important control mechanism. A number of substances have been found to affect angiogenesis. Those substances that inhibit or moderate undesired angiogenesis, particularly angiogenesis linked to disease conditions of the retina (retinopathy), are preferred for use in the compositions of this invention. Preferred compositions of this invention comprise more than one chemical type of angiogenesis regulator or more than one source of an angiogenesis regulator. Different regulators are believed to function in a complimentary manner to achieve a biochemical balance. In addition, components of the compositions, other than specifically listed neovascular agents, may also affect angiogenesis. For example, antioxidants and free-radical scavengers can control free radicals which, by various mechanisms, may destroy angiogenesis regulation. The control of oxidative stress due to antioxidants may have a significant effect on beneficial neovascular control, particularly in the biological states that lead to retinopathy. As discussed above regarding antioxidants, conservative doses of several angiogenic regulators are believed to be more beneficial, i.e., enhanced effectiveness with minimal potential for toxic effect, than larger doses of a single chemical.

[0411] Cartilage, an avascular tissue, is a source of angiogenesis inhibitor(s). Shark and bovine cartilage, among others, are sources of angiogenesis inhibitor and may provide collagenase inhibition as well. Chondroitin sulphate, a mucoploysaccharide found in most mammalian cartilaginous tissues and shark cartilage, is believed by many to be the most active angiogenesis regulating component of Shark Cartilage. The restoration of diabetic depleted chondroitin sulphates may also affect collagen stabilization which would help to normalize the collagen matrix of vascular tissue and therefore create a more stable vascular structure. Chondroitin sulphate can be provided in a number of forms with different counterions, e.g., sodium, potassium, etc. Sodium chondroitin sulphate is the form preferred for use in compositions of this invention.

[0412] Protamine sulphate is a mixture of the sulphates of basic peptides that can be prepared from the sperm or the mature testes of certain species of fish. It is an arginine rich basic protein which has been shown to be a specific inhibitor of angiogenesis, possibly due to its ability to bind to heparin. Protamine has been used in some insulin preparations to prolong the effects of insulin. Protamine is usually given as the sulphate, but the hydrochloride form may also be used.

[0413] Genistein as well as daidzein are plant-derived isoflavonoids, found for example in soybeans, that exhibit an ability to inhibit neovascularization by controlling endothelial cell proliferation in vitro. Soy isolate is a natural source of genistein, daidzein or the glycoside derivatives (e.g., genistin, diadzin and sophoricoside) of these isoflavones. Soy isolate also provides nutritional benefit and may supplement depleted amino acids.

[0414] Heparin sulphate levels are increased in diabetics while levels of chondroitin sulphates are decreased. This suggests an imbalance in chondroitin sulphate and in angiogenic regulation. Gymnema Sylvestre which normalizes heparin levels is provided in the compositions of this invention, at least in part, to affect heparin levels which in turn may affect angiogenic regulation due to shark cartilage and protamine sulfate which both bind to heparin. The insulin/glucose stabilization effects of Gymnema sylvestre would reduce the oxidative stress that contributes to the neovascularization factors described above.

[0415] Collagen Factors

[0416] Restoration of the collagen matrix in vascular and other tissue is an important aspect of the formations of this invention. In this regard, building blocks for collagen synthesis, growth regulators related to collagen synthesis and repair, cofactors for synthesis of collagen, calcium binding

and/or regulatory agents and nutrients including various minerals associated with promotion of collagen synthesis are provided in formulas of this invention. Glucosamines stimulate and provide building blocks for collagen synthesis. Chondroitin sulphate is a glucosamine that functions for growth regulation and stimulates collagen synthesis. Glucosamine sulphate is a preferred glucosamine for promoting collagen synthesis and repair.

[0417] Manganese is a cofactor which promotes collagen synthesis. Amino acids, particularly branched chain amino acids, provide protein for synthesis of collagen.

[0418] Other components that affect collagen synthesis are inhibitors of mammalian collagenases and antioxidants. Inhibition of collagen breakdown by oxidative stress or by enzymatic degradation combined with stimulation and prevention of collagen synthesis is believed to result in improved vascular condition.

[0419] Minerals

[0420] The compositions of the present invention include various minerals including zinc, chromium, calcium, magnesium, potassium, manganese, and selenium. Optional additives can include other minerals, chromium in non-diabetic formulations, which may have beneficial or nutritional value for a given individual, particularly those minerals that are depleted in a given individual with diabetes. Certain minerals can have additional therapeutic value in the compositions of this invention. For example as discussed above zinc is believed to play a significant role as an antioxidant and many diabetics are found to have a zinc deficiency, especially those with retinopathy.

[0421] In general, minerals can be provided in a variety of forms with various counterions. The choice of a given form of mineral will depend generally on the type of dosage form that is employed, whether, for example, an oral or intravenous dosage form is employed. Preferred forms of minerals are generally those that are more absorbable and those that have lower toxicity. In addition, preferred forms will be generally compatible with the other components of a given mixture, will result in minimal irritation or other undesired side effects. Choices of form of a given mineral provided in a given composition of this invention will also depend on the other ingredients in the composition, particularly to avoid excessive levels of a given counter ion.

[0422] Zinc can be provided in a variety of forms and with various counter ions, including among others zinc citrate, zinc fumarate, zinc gluconate, zinc alpha-ketoglutarate, zinc lactate, zinc malate, zinc succinate, zinc picolinate or mixtures thereof. The preferred form of zinc in the compositions of this invention is zinc (Krebs) in which the counter ions are a mixture of the anions of the five primary organic acids of the tricarboxylic acid cycle (Krebs Cycle) i.e., a mixture of the zinc salts of citric, fumaric, malic, alpha-ketoglutaric and succinic acids.

[0423] Chromium can be provided by a variety of dietary sources including, among others, brewer's yeast, liver, potatoes with skin, beef, fresh vegetables and cheese. Chromium exists in a dinicotino-glutathionine complex in natural foods. Such dietary and natural materials can provide sources of chromium for use in compositions of this invention. As with other minerals there are generally a variety of forms of chromium that are useful in the compositions of this invention including for example, chromium sulphate. Chromium picolinate is particularly preferred for use in this invention because picolinate forms of minerals are generally transported more quickly and efficiently in the body.

[0424] Magnesium can be provided in a variety of forms and with various counter ions, including among others magnesium citrate, magnesium fumarate, magnesium gluconate, magnesium alpha-ketoglutarate, magnesium lactate, magnesium malate, magnesium succinate, magnesium picolinate, magnesium sulphate or mixtures thereof. Preferred forms of magnesium in the compositions of this invention are magnesium malate magnesium (Krebs) in which the counter ions are a mixture of the anions of the five primary organic acids of the tricarboxylic acid cycle (Krebs Cycle) i.e., a mixture of the magnesium salts of citric, fumaric, malic, alpha-ketoglutaric and succinic acids.

[0425] Calcium can be provided in a variety of forms and with various counter ions, including among others calcium ascorbate, calcium carbonate, calcium citrate, calcium fumarate, calcium gluconate, calcium alpha-ketoglutarate, calcium levulinate, calcium lactate, calcium malate, calcium succinate, calcium picolinate or mixtures thereof. Calcium can also be provided in a variety of natural sources including dolomite, oyster shells, and bone meal. The more preferred form of calcium in the compositions of this invention is calcium (Krebs) in which the counter ions are a mixture of the anions of the five primary organic acids of the tricarboxylic acid cycle (Krebs Cycle) i.e., a mixture of the calcium salts of citric, fumaric, malic, alpha-ketoglutaric and succinic acids. Also preferred for use in compositions of this invention are calcium carbonate, and calcium citrate which are noted for being highly absorbable.

[0426] Potassium can be provided in a variety of forms and with various counter ions, including among others potassium citrate, potassium carbonate, potassium fumarate, potassium gluconate, potassium alpha-ketoglutarate, potassium lactate, potassium malate, potassium succinate, potassium picolinate or mixtures thereof. The preferred form of potassium in the compositions of this invention is potassium citrate which has one of the highest levels of elemental potassium.

[0427] Manganese, selenium, and strontium can be provided in a variety of forms with various counterions. Selenium is preferably supplied as an organoselenium compound, e.g., selenomethionine. Manganese asparate is a preferred form of manganese for use in the formulas of this invention.

[0428] Ranges of zinc (Krebs), calcium (Krebs), magnesium (Krebs), chromium picolinate, potassium citrate and other minerals in an average daily dose of a composition of this invention are provided in Table 3. The ranges given are maximum ranges which may need to be adjusted dependent upon the amount and form of other ingredients included in the composition. These ranges can be readily adjusted by those of ordinary skill in the art of nutrient and therapeutic formulation to other forms of the minerals noted above.

[0429] A mineral complex can optionally be combined with the compositions of this invention in addition to or substituted for specific minerals in the various formulas. Preferably, the mineral complex is used to supplement nutritional minerals not already included in specific formulation. A preferred mineral complex includes absorbable salt or chelated forms of:

[0430] major mineral components: calcium, magnesium, and potassium also chloride (e.g., as potassium chloride) and sulphate (e.g., as manganese sulphate);

[0431] intermediate level components: zinc, manganese, boron and copper;

[0432] minor components: chromium, selenium, iodine, molybdenum, vanadium, lithium, rubidium, silicon (as silica), nickel, phosphorus, strontium and cadmium;

[0433] trace minerals: preferably from natural sources e.g., marine organic minerals or sea water concentrate.

[0434] The minerals may be provided in a variety of salt and complex forms, i.e., as the salts of Krebs cycle acid anions: aspartate, citrate, fumarate, malate and/or succinate salts; as salts of amino acids (e.g. arginates); as picolinate salts; as ascorbate salts, as nicotinate salts. Silicon is preferably provided as the trisillicate anion, e.g. magnesium trisillicate. Selenium is preferably provided as organoselenium compound, e.g. selenomethionine. A variety of natural sources of minerals are known to the art including plant extracts, and can be used to provide minerals in the formula of this invention. A preferred mineral complex is:

[0435] Calcium (Krebs, lactate, aspartate, arginate, etc.)

MINERAL COMPLEX	
Calcium (Krebs) (lactate, aspartate, argininate etc.)	10 mg to 10,000 mg
Magnesium (Krebs), (aspartate, argininate, triscilicate (malate), etc.)	3 mg to 10,000 mg
Potassium (Krebs) (argininate, aspartate)	2 mg to 10,000 mg
Zinc (Krebs) (picolinate)	1 mg to 100 mg
Manganese (Krebs)	10 mcg to 100 mg
Boron (gluconate)	0 mcg to 100 mg
Copper (Krebs)	10 mcg to 50 mg
Chromium (picolinate, nicotinate, etc.)	2 mcg to 50 mg
Selenium (l-selenomethionine)	1 mcg to 50 mg
Iodine (marine organic minerals, kelp, etc.)	1 mcg to 50 mg
Molybdenum (Krebs)	1 mcg to 50 mg
Vanadium (Krebs)	1 mcg to 50 mg
Lithium (aspartate, argininate, etc.)	1 mcg to 50 mg
Rubidium (Krebs)	1 mcg to 50 mg
Silica (sodium melasilica, magnesium trisilicate)	10 mcg to 200 mg
Trace minerals (marine organic minerals)	10 mcg to 200 mg
Cobalt	10 mcg to 200 mg
Nickel	1 mcg to 50 mg
Phosphorus (e.g., dicalcium phosphate)	1 mcg to 50 mg
Chloride (e.g., potassium chloride)	1 mg to 1,000 mg
Sulphur (manganese sulphate)	10 mcg to 100 mg
Strontium	1 mcg to 800 mg
Cadmium	1 mcg to 500 mg

[0436] Minerals specifically included in a given formulation of this invention are preferably provided at the level indicated in that formulation. For an individual diagnosed with a particular mineral deficiency (e.g., iron deficiency), dosages of a given mineral may be increased as needed and additional minerals, e.g. iron, may be added to the mineral complex.

[0437] Vitamins

[0438] Vitamins are included in compositions of this invention to provide supplementation for depletion and dietary deficiencies and in some cases for specific therapeutic benefits. Vitamins may also complement the activity of other components of the composition. Vitamin C, i.e., ascorbic acid, vitamin E, i.e., alpha-tocopherol, and vitamin A provide general nutritional supplementation as well as antioxidant function, as discussed above. Vitamin B6, i.e., pyridoxine, vitamin B12, i.e., cobalamine, and folic acid (folate) provide general nutritional supplementation, and more specific benefits. Folate and vitamins B6 and B12 have antianemia properties. Recent studies suggest that these vitamins may also be helpful in lowering blood levels of homocysteine, an amino acid that has been associated with increased risk of heart disease. Vitamin B2, i.e., riboflavin, provides general nutritional supplementation.

[0439] A Vitamin B complex can be employed in addition to or substituted for Vitamin B components of the formulas of this invention. A preferred Vitamin B complex includes:

Vitamin B1 (thiamine)	10 μg–100 mg	(10%))
Vitamin B2 (riboflavin)	10 μg–50 mg	(5%)
Vitamin B3 (nicotinamide or niacinamide, preferably as niacinamide ascorbate)	1 mg–1,000 mg	(53%)
Vitamin B5 (pantothenic acid)	1 mg–200 mg	(26%)
Vitamin B6 (pyridoxine HCl)	10 μg–3 mg	(5%)
Vitamin B12 (cyanocobalamin)	1 μg–200 μg	(0.03%),

[0440] where a preferred range and preferred specific relative amounts of the components are given.

[0441] Amino Acids

[0442] The formulas of this invention include amino acids that have a particular therapeutic function. Formulas of this invention may also contain additional amino acids for nutrient supplementation or for compensation for an individual's deficiency. Compositions of this invention can include any of the following: alanine, arginine, aspartic acid, cystine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, carnitine (all in the biologically active L-form) and gamma aminobutryic acid. When present in a given formula, a specifically listed amino acid is preferably provided in the amount needed to provide the desired therapeutic effect. Additional nutritional amino acids are preferably provided in an nutritionally effective amount.

[0443] Other Components

[0444] Fenugreek (*Tigonella foenumgraecum L. Leguminosae*) is an annual herb, the seeds of which contain a number of alkaloids, including trigonelline and coumarine, and the steroidal sapogenin, diosgenin. Fenugreek seeds reduce serum cholesterol levels in animals. In particular, the defatted fraction of fenugreek seed which is rich in fiber (about 54%) and contains about 5% of steroidal sapogenin, including diosgenin significantly lowers plasma cholesterol, blood glucose and plasma glucagon levels. Fenugreek is included in certain preferred compositions of this invention for treatment of diabetic complications for its hypoglycemic effect. The preferred form of fenugreek for formulations of this invention is the defatted, fiber-rich fraction.

[0445] Source of Omega-3-Fatty Acids

[0446] Omega-3 oils are a family of oils having relatively high concentrations of omega-3 polyunsaturated fatty acids,

including eicosapentaenoic acid (EPA) and alpha-linolenic acid. These oils exhibit a hypolipidaemic action, especially a reduction in plasma triglycerides linked to a reduction in very-low density lipoproteins (VLDL). They also lower high fibrinogen levels which have been linked to risk of cardiovascular disease. They also exhibit anti-inflammatory and anti-platelet effects. Fish oils and other marine oils typically contain high levels of omega-3-fatty acids. In general, omega-3-fatty acids are believed to reduce blood pressure, and lower cholesterol and triglyceride levels. Omega-3 fatty acids are found in a variety of naturally-occurring sources and may be provided in their acid form or as fatty acid salts or fatty acid esters.

[0447] Chronic omega-3-fatty acid deficiency correlates with chronic nephropathic injury. EPA and DHA (docosahexanoic acid) produce an anti-inflammatory effect by reducing prostaglandin production and displacing arachidonic acid. HDL, triglycerides and fibrinogen have also been successfully reduced by omega-3-oils.

[0448] Flaxseed (also called Linseed) is a nutrient rich in omega-3-fatty acids. It is a major source of alpha-linolenic acid (an omega-3-fatty acid) and lignin. Ground flaxseed is a preferred source of omega-3-fatty acids over fish oils for use in compositions of this invention. The use of flaxseed oils avoids the potential toxicity that has been associated with long term use of fish oils. Fish and marine oils or individual omega-3-fatty acids, including EPA, and ALA (and their analogous fatty acid esters) can be used in these formulations in place of flaxseed.

[0449] EPA ethyl ester has been shown to reduce microalbuminuria in diabetics. Reduction in microalbuminuria may prevent or slow the development of nephropathy.

[0450] Essential fatty acids (EFAs) are those fatty acids that cannot be made by the body and must be supplied through the diet. Fresh, poly-unsaturated vegetable oils are a major source for EFAs (linoleic, linolenic and appropriate levels of arachidonic acids). EFAs have a variety of beneficial effects including reduction of blood pressure, lower cholesterol, and lower triglyceride levels. Linolenic acid is the preferred essential fatty acid for formulations of this invention. A natural source of linolenic acid is Evening Primrose Oil which also provides high levels of GLA (about 9%) with minimal toxic properties.

[0451] Coenzyme Q_{10}, also designated ubiquinone(50) is one of a group of benzoquinones involved in electron transport. Coenzyme Q_n, where n=1-12, has a 2,3-dimethoxy-5-methylbenzoquinone nucleus with various terpenoid side chains. Coenzyme Q with 10 isoprene units (Coenzyme Q_{10}) is the most common form in animals. Coenzyme Q_n, where n=6-10, are naturally occurring. Coenzyme Q_{10} is a necessary component of the energy-generating process of every cell in the body. Coenzyme Q_{10} can also function as an antioxidant. Coenzyme Q_{10}, the preferred form of coenzyme Q for human nutrition and therapy, is provided in formulations of the present invention to supplement nutritional deficiencies, particularly in diabetics, which are believed to generally exacerbate disease conditions and cause fatigue. Certain commonly-used oral diabetes drugs, including Tolazamide and Phenformin, may interfere with the enzymes that use Coenzyme Q_{10}, and thus worsen pre-existing deficiencies in diabetics. Adequate tissue reserves of Coenzyme Q_{10} may also facilitate blood sugar regulation. Coenzyme Q_{10} is also believed to generally enhance an individual's energy levels. Other forms of coenzyme Q, particularly coenzyme Q_n, where n is 1-9 and 10-12 and more preferably the naturally-occurring forms where n=6-9, can be employed in place of coenzyme Q_{10} in the formulas of this invention.

[0452] Taurine is found in high concentrations in the brain, retina and kidney cortex. Taurine deficiency has been linked to retinal pathologies. Taurine deficiency has also been found in diabetics. Taurine may have a protective effect on retinal tissue and/or act as an antioxidant. Taurine has been linked to inhibition of platelet aggregation and atherosclerotic lesions and has been found to help control blood pressure. Taurine can be provided from a variety of sources in different forms. Homotaurine, a taurine precursor, is a good bioavailable oral form to provide taurine. Compositions herein can contain taurine or homotaurine.

[0453] L-Carnitine is an essential co-factor of fatty acid metabolism. Significantly decreased plasma carnitine levels are common in insulin dependent diabetics including those with nephropathies. This implies that such patients may suffer from inadequate ATP reserves that could cause fatigue and oxidative stress due to reduced lipid metabolism caused by faulty transport of fatty acids across mitochondrial membranes. Carnitine supplementation supports increases in fat utilization and oxygen uptake while decreasing plasma lactate levels and respiratory quotients. Carnitine has been shown to reduce ketones, LDL and triglycerides and increase HDL while acting as a vasodilator. Low carnitine levels may correlate with low plasma albumin and edema. L-Carnitine can be provided as N-acetyl-l-carnitine hydrochloride, the preferred form for this invention. Carnitine can be also be provided as the 1- or d,1-form as hydrochloride or other salts.

[0454] Phytosterols, including plant sterols, which comprise beta-sitosterol, campesterol, and/or stigmasterol have been shown to reduce the absorption of the LDL cholesterol component of foods in the gut on a dose dependent basis of approximately one-to-one sterols to cholesterol, while enhancing beneficial HDL to positively effect the LDL-HDL Ratio. An additional benefit of blocking cholesterol absorption is that it frees other ingredients in the formulation of this invention to eliminate existing cholesterol plaque (See Table 4). This reduces the added burden of combating the new plaque development of cholesterol which would not otherwise have been blocked by the plant sterols. Plant sterols have been shown to primarily block harmful LDL cholesterol and admit beneficial HDL cholesterol, the levels of which can actually be elevated. Plant sterols can be provided in the formulas of this invention in soy oil or by addition of individual sterol components. A commercially available mixture of phytosterols, "Cholestatin III" (about 62% beta-sitosterol, about 24% campesterol and about 14% stigmasterol), produced in bacterial fermentation, is preferred for use in the formulas of this invention. Saw palmetto is another useful source of phytosterols.

[0455] The inhibition of the absorption of dietary cholesterol can also be enhanced by administration of epigallocatechin gallate found in Green Tea Extract to promote excretion of cholesterol.

[0456] Gymnema sylvestre

[0457] Gymnemic acid, the active ingredient in Gymnema sylvestre, suppresses sensitivity to sugar and its absorption,

thereby reducing blood glucose levels. It also restores the levels of three chondroitin sulfates which may assist in collagen repair and/or aid in angiogenesis regulation. Heparin sulphate levels are increased in diabetics while three chondroitin sulfates are decreased. Gymnema sylvestre which normalizes heparin levels could play a supporting role in the angiogenic regulation of other ingredients in this formulation, namely shark cartilage and protamine sulfate. Both are angiogenic regulators which bind to heparin. The restoration of depleted chondroitin sulfates probably plays a role in collagen stabilization which would help to normalize the collagen matrix and therefore create a more stable structure upon which angiogenesis regulation could more easily exist. The insulin/glucose stabilization effects of Gymnema sylvestre would reduce the oxidative stress that contributes to the neovascularization factors described above.

[0458] Allicin is reported to be the active ingredient of garlic and garlic preparations that have been associated with cholesterol and triglyceride reduction. Consumption of garlic has been associated with increased fibrinolysis, reduced platelet aggregation and vasodilation, but clear clinical effect reducing morbidity and mortality in cardiovascular disease has not demonstrated (*British Med. J.* (1991) 303:379-380; Grunwald, J. (1990) *J. British Pharmacol.* 28:582-583).

[0459] Aloe vera is suggested to be an inhibitor of thromboxane A_2 and useful as an oral and topical agent for wound healing (Davis, R. H. (1989) J Amer. Podiatric Medi. Assoc. 79(11):559-562 and Heggers, J.P. (1993) Phytotherapy Research 7:S48-S52.) Aloe vera is included in oral dosage forms of the formulas of this invention as well as in wound ointment formulation.

[0460] Calcitonin (Merck Index, Ninth Edition (1976) 1633 P.208) is a calcium regulating hormone secreted by mammalian thyroid gland that is employed in the treatment of bone disorders including osteoporosis. Amylin (see U.S. Pat. No. 5,405,831) is a peptide found in amyloid deposits of diabetics (Type 2), which may be a peptide hormone having a role in storage and disposal of food as carbohydrate and fat. Amylin increases liver output of glucose, increases lactate production in muscle and decreased insulin action. U.S. Pat. No. 5,405,831 reports that amylin, variants of amylin and amylin agonists are useful, like calcitonin, for the treatment of bone disorders to prevent or inhibit bone resorption because of its role in calcium metabolism.

[0461] Centella asiatica is a plant traditionally used in wound healing. An extract, preferably titrated extract (TECA) or total triterpene fraction containing triterpenes, including asiatic acid, can be used in wound healing. Asiatic acid is reported to stimulate collagen synthesis in cell cultures (Maquart, F-X et al. (1990) *Connective Tissue Res.* 24:107-120 and Tenni, R. et al. (1965) *Ital. J. Biochem.* 240:3944-3950).

[0462] Sulphated saccharides and salts thereof are reported to be useful as an ingredient in topical preparations to the teeth or gingiva for prophylaxis or treatment of diseases of the tooth or tooth-supporting tissue (U.S. Pat. No. 5,240,710). Sulphated saccharides include polysulphated saccharides and persulfated saccharides, for example, sucraflate, which is sucrose octakis (hydrogen sulphate) aluminum complex, or a salt of sucrose octakis (hydrogen sulphate). Polysulfated saccharides have also been suggested to stimulate neovascularization at skin wound sites, but have also been associated with increased inflammation at the wound site (EP 230,023 (1987)).

[0463] Vitamin D3 is associated with calcium transport and bone calcium resorption. 1,25-dihydroxy Vitamin D3 is reported to lower blood pressure and increase sensitivity to insulin. Certain analogs and derivatives of 1,25-dihydroxy Vitamin D3 are reported to induce minimal or no hypercalcemia. (Hypercalcemia is a significant contributing factor to the toxicity of Vitamin D's.) Derivatives, such as 22-oxa-Vitamin D3 is thus indicated to have reduced toxicity compared to Vitamin D3. See: Abe, J. et al. (1991)*Endrocrinology* 129:832-837 and Mark, R. (1992) *Pediatric Nephrology* 6:345-348. Vitamin D3 is also reported to be important in cell differentiation. The inventor includes Vitamin D3, particularly lower toxicity Vitamin D3 analogs (22-oxa-Vitamin D3) in the formulas of this invention as a calcium regulator that is a factor for promotion of collagen synthesis and more importantly for its additional function in the immune response which is believed will reduce immune attack on endothelial tissue to reduce atherosclerosis and its lesions.

[0464] Vitamin K1

[0465] Vitamin K is a cofactor involved in blood coagulation. Vitamin K1, or phylloquinone, is a preferred from of Vitamin K for use in the formulas herein. Vitamin K is also reported to increase calcium binding affinity of certain proteins in bone formation. Vitamin K is included in formulas of this invention to supplement any vitamin or cofactor deficiency and for its calcium binding function which indicates usefulness in tissue regeneration. Vitamin K is preferred for addition in formulations for treatment and prevention of dental and gum disorders, particularly gingivitis.

[0466] Betain HCl, Pepsin and Sodium Bicarbonate

[0467] Inappropriate acidity is believed to be a factor in the pathogenesis of chronic disease. Mitochrondrial antagonism resulting in oxidative stress is a probable mechanism. betain, HCl, pepsin and sodium bicarbonate have all demonstrated the ability to help regulate hyperacidity. In addition, betain HCl and pepsin are among digestive enzymes often deficient in the elderly as well as chronic disease sufferers. Supplementation of these digestive enzymes to those having this deficiency increases the availability of nutrients contained in the food they eat.

[0468] The proposed function of components listed in the specific formulas of this invention and stated to be options herein are discussed above, are specified in Tables 1 and 2 or are known to those of ordinary skill in the art.

[0469] Table 4 provides compositions of preferred formulations of this invention particularly useful for ameliorating symptoms and conditions that are the complications of diabetes mellitus, including retinopathy and nephropathy. These formulations are further described in Example 1. The specific amounts of given components are listed in the Table as an average daily adult dose. Where appropriate the active amount of a given component, which relates to the amount of active ingredient in the particular component listed, is provided.

[0470] Compositions in which the specific daily adult dosage of individual components varies from those listed in Table 4 for the preferred embodiment (or the dosages of active ingredients listed) by less than about 10% are preferred for use in treatment of retinopathy and nephropathy. Compositions in which the specific dosages vary from those listed in Table 4 by less than about 20% are more preferred for use in treatment of retinopathy and nephropathy. The dosages listed in Table 4 were calculated for a preferred dosing schedule of "6 days on, 1 day off" (no nutrient/medication being taken on the seventh day). Dosages can be readily adapted for other dosing schedules by those of ordinary skill in the art. For example, the dosages of Table 4 are reduced by ⅙th for use in a "7 days on" schedule. Preferred dosing schedules of this invention include periodic "days off" the composition to avoid development of the peroxidative state and avoid excessive build-up of antioxidants. Dosing schedules as well as dosage can be readily adjusted for individual needs.

[0471] Listed in Table 3 is a broad effective dose range (daily adult dose) for individual active components of the formulas of this invention. The broad dose range given in the table provides guidance regarding approximate minimal effective amounts of given components from any source and guidance for dosage of equivalents. The maximum dosages listed are estimates based generally upon what is known in the art concerning the individual components listed. The maxima listed may merely be based on an estimate of maximum amount that can be practically provided in a daily oral dosage form. Those of ordinary skill in the art will appreciate that the dosages listed in Table 3 are specific for the forms and sources of components listed. Dosages can be readily adapted by those of ordinary skill in the art for use of alternate forms or sources of the components listed or for use of functional equivalents.

[0472] Tables 1 and 2 provide a summary of the general biological functions of most components that are believed to be beneficial for the treatment of disorders and conditions associated with macroangiopathy and microangiopathy. This listing provides the inventor's current understanding of the functions provided by components included in the preferred composition and provides guidance for the choice of alternative components with similar functionality. The inventor, however, does not wish to be bound by the specific functional correlations listed in these tables or by proposed functionality of individual activity. The etiology of the diseases and conditions discussed herein is complex and a given component of a formula of this invention may have several different effects. In some cases, the component listed in the table is itself a mixture, for example, pine bark extract is a mixture of naturally occurring compounds. In these cases, different components of the listed mixtures may contribute to different functions listed in Tables 1 and 2.

[0473] The compositions of this invention specifically ameliorate diabetic complications including retinopathy and nephropathy. The formulas of this invention are effective in the treatment and prevention of complications associated with both Type I and Type II diabetes. The diagnosis and symptoms of these disorders and complications are understood in the medical arts and a variety of methods are known in the art to evaluate the severity and extent of the conditions. Amelioration of symptoms of retinopathy and nephropathy can be measured by any such methods or procedures known in the art.

[0474] The compositions of this invention specifically ameliorate disease conditions of the retina including retinopathy, macular degeneration and cataracts. The diagnosis and symptoms of these disorders and complications are understood in the medical arts and a variety of methods are known in the art to evaluate the severity and extent of the conditions. Amelioration of symptoms of retinal degeneration and related retinal disorders can be measured by any such methods or procedures known in the art.

[0475] The compositions of this invention specifically ameliorate neuropathy. The diagnosis and symptoms of this disorder are understood in the medical arts and a variety of methods are known in the art to evaluate the severity and extent of this condition. Amelioration of symptoms of neuropathy can be measured by any such methods or procedures known in the art.

[0476] The compositions of this invention specifically ameliorate macrovascular disorders including cardiovascular disease. Cardiovascular disease includes atherosclerosis, the formation of vascular and coronary lesions, and a variety of related conditions. The diagnosis and symptoms of these disorders are understood in the medical arts and a variety of methods are known in the art to evaluate the severity and extent of the conditions. Amelioration of symptoms of cardiovascular disease can be measured by any such methods or procedures known in the art.

[0477] The compositions of this invention are useful in the treatment of slow-to-heal or recurrent wounds, specifically those wounds that are associated with diabetes, and specifically those wound in which infection is not the major cause of the failure to heal. The diagnosis and symptoms of this disorder are understood in the medical arts and a variety of methods are known in the art to evaluate the severity and extent of the conditions. Amelioration of recurrent wounds and the increased speed of healing of such wounds can be measured or assessed by any such methods or procedures known in the art.

[0478] The compositions of this invention are useful in the treatment and prevention of dental and periodontal disorders, including gingivitis. The diagnosis and symptoms of these disorders are understood in the dental and medical arts and a variety of methods are known in the art to evaluate the severity and extent of the conditions. Amelioration of these disorders can be measured or assessed by any such methods or procedures known in the art.

[0479] The following example illustrates this invention and is in no way intended to limit the scope of the invention.

EXAMPLE 1

[0480] A Nutrient and Therapeutic Composition for Improving the Symptoms of Diabetic Retinopathy and Nephropathy

[0481] Preferred nutrient and therapeutic composition of this invention are formulas A and B containing the components listed in Table 1 in the dosage amounts listed for "Average Adult Dose Per Day". The amounts listed are of the active ingredient, unless otherwise noted. The active

ingredient may be provided in a variety of forms containing more or less active ingredient than the forms employed specifically in A or B.

[0482] The following sources of ingredients listed in Table 1 were employed:

[0483] Bilberry extract, as a dry hydroalcohol extract containing anthocyanosides corresponding to 25% (by weight)of anthocyanidines obtained from Indena (Milan, Italy). Grape Seed Extract (leucocyanidins) (90-100% OPCs) was also obtained from Indena (Milan, Italy).

[0484] Pine Bark Extract (OPC 90%) was obtained from Euromed (Barcelona, Spain).

[0485] Green tea polyphenols (95%, min. 75% catechins, low caffeine) was obtained from TSI, International, Inc. (New York, N.Y.).

[0486] N-Acetyl-l-cysteine (99%), L-carnitine base (Product No. 18-1870-00), CoQ10 (ubidecarenone), 1-(+)-ascorbic acid, riboflavin (USP, FCC, Water CAS 7732-18-5 max 1.5%), pyridoxine hydrochloride (USP, FCC), and vitamin B12 (USP) were obtained from Schweizerhall, Inc. (Piscataway, N.J.). Vitamin B12 (cyanocobalamine was diluted in inactive filler to give a 1% by weight mixture). Acetyl-R-carnitine is available from several manufacturers.

[0487] Vitamin A acetate (T-500A) was obtained from Hoffmann-La Roche (Belvidere, N.J.).

[0488] Taurine (98.5% min.) and folic acid (USP) were obtained from Seltzer Chemicals, Inc. (Carlsbad, Calif.). Homotaurine is available from several manufacturers.

[0489] Linolcic Acid (1High Purity, 99% min) was obtained from Spectrum Quality Products (Gardena, Calif.).

[0490] Lipoic Acid (99.8%) and protamine sulphate (USP) were obtained from Maypro Industries, Inc. (Harrison N.Y.).

[0491] Lutein is provided in a nutrient composition "FloraGlo" Lutien (Trademark, Kemin Industries, Des Moines, Iowa) comprising 5% by weight lutein and 0.22% zeaxanthin. This material is in beadlet form and also comprises vegetable oil, natural vitamin E (as a preservative), rosemary, natural citric acid, gelatin, sucrose and starch. See U.S. Pat. No. 5,382,714.

[0492] Chondroitin sulphate as the sodium salt produced by the Strandberg method from beef trachea was obtained from Weinstein Nutritional Products (Irvine, Calif.).

[0493] Chromium picolinate "Chromax" was obtained from Nutrition 21 (San Diego, Calif.).

[0494] Calcium (Krebs)22%, Zinc (Krebs) 30% and Magnesium (Krebs) were obtained from Monarch Nutritional Laboratories (Ogden, Utah).

[0495] Potassium citrate (NF granular) complying with USP, FCC and FAO/WHO Food additive specifications was obtained from Archer Daniels Midland.

[0496] Shark cartilage powder (100%, 200 mesh) was obtained from Global Trading (USA) Inc. (Union, N.J.).

[0497] Isolated soy protein ("Supro" HD90, Trademark) was obtained from Protein Technologies International (St. Louis, Mo.). Isolate soy protein products from this source are reported to typically contain (in mg/g protein) 0.15 to 0.72 mg daidzein, 0.48 to 1.51 mg genistein, 0.05 to 0.26 glycitein with a total isoflavone content of 0.68 to 2.49 mg (aglucone units adjusted for molecular weight).

[0498] Phytosterol complex, "Cholestatin III" can be obtained from several sources.

[0499] Vitamin E, d-alpha-tocopheryl acetate (natural source, powder) was obtained from B&D Nutritional Ingredients, Inc. (Carlsbad, Calif.).

[0500] Flax seed powder containing about 23 mg of alpha-linolenic acid (omega-3-fatty acid) per 100 grams powder was obtained from Honeyville Grain Inc. (Salt Lake City, Utah).

[0501] Fenugreek seed powder was obtained from Botanicals International (Long Beach, Calif.).

[0502] Ginkgo biloba L. powder extract about 26% flavonglycosides and Gymnema sylvestre powder were obtained from Motherland International Inc. (Chino, Calif.).

[0503] Those of ordinary skill in the art of formulation of nutrients and therapeutic compositions will appreciate that components functionally equivalent to those specifically disclosed herein, as well as alternative forms and sources in addition to those specifically disclosed herein for individual composition ingredients are available. This invention is intended to encompass all such functional equivalents and alternatives that are readily known to the art.

TABLE 1

Summary of Functions of Components of Compositions of this invention for Microangiopathy and Macroangiopathy

Primary formulas comprise components which:
1. Function as antioxidant to control oxidative stress;
2. Function as neovascular regulators controlling angiogenesis to promote vascular healing and integrity;
3. Stabilize glucose and amylase factors, for example, to increase glucose tolerance in diabetes; and
4. Supplement dietary deficiencies and loss through spillage, particularly as associated with diabetes.

Compositions of this invention can further comprise components which:
5. Stabilize insulin supply and decrease sensitivity to glucose;
6. Stabilize protein factors, control proteinuria, glycosylation and albumin;
7. Control anti-sclerotic factors, functioning as/to:
   - A. Anti-platelet or anti-thrombic agents
   - B. Homocysteine inhibitors
   - C. Reduce atherosclerotic lesions
   - D. Reduce LDL and VLDL
   - E. Improve HDL/LDL ratio
   - F. Inhibit lipoprotein (a) production
   - G. Inhibit cholesterol absorption in bowel
   - H. Enhance cholesterol excretion
   - I. Triglycerides inhibitors
   - J. Fibrogen inhibitors
   - K. Nitric Oxide inhibitors (Optional)
   - L. Ketosis regulators
8. Reduce immune phagocytic response to:
   - A. Leukotrienes, neutrophils, etc.
   - B. Immunoglobulin (a)
9. Reduce and stabilize anti-hypertensives as:
   - A. Angiotensin converting enzyme inhibitors & vasodilators
   - B. Prostacyclin inhibitors
   - C. Aldose Reductase inhibitors
   - D. Blood pressure inhibitor/regulator (systolic only)
   - E. Agents to reduce blood pressure during bowel contractions
   - F. Anti-edema agent
   - G. Histamine suppressors
10. Enhance cellular or metabolic function, for example for:
   - A. Glutathione restoration

TABLE 1-continued

Summary of Functions of Components of Compositions of this invention for Microangiopathy and Macroangiopathy

B. ATP/NAD restoration
11. Promote vascular healing and integrity by:
A. Restoring the collagen matrix
B. Histamine suppression (Optional)
12. Promote better nutrient digestion and absorption
13. Improve pH factor by controlling digistens and systemic hyperacidity
14. Participate in collagen synthesis
15. Calcium regulator
16. Control myocardial infarction and damage
17. Increase cardiovascular exercise ability and tolerance
18. Increase other antioxidants, including Vitamin E, reduced glutathione, uric acid, superoxide dismutase (SOD), catalyze, or glutathione peroxidase
19. Inhibit breakdown of myocardial cell membrane
20. Provide immune differentiation
21. Restore Vitamin E levels by intestinal absorption of omega-3-fatty acids
22. Improves cell transport and mitochondrial function
23. Improves sleep for better disease resistance and recovery
24. Amino acid believed to inhibit or ameliorate diabetes pathogenesis
25. Amino acid believed to inhibit or ameliorate cardiovascular pathogenesis
26. Amino acid believed to contribute to wound healing or prevention
27. Amino acid believed to inhibit or ameliorate neuropathic pathogenesis
28. Amino acid believed to inhibit or ameliorate dental and periodontal pathogenesis
29. Promoter of DNA polymerase for wound healing
30. Provides protein sources for wound healing
31. Contributes to improved bone density
32. Promotes anti-caries and anti-gingivitis environment
33. Accelerates wound healing

[0504]

TABLE 2

Formula Components	Functions Functions Listed in Table 3
Pine Bark Extract	1, 7D, 8A, 9A, 9F, 9G 14, 32, 33
Bilberry Extract	1, 9A, 11, 14
Grape Seed Extract	1, 7D, 8A, 9A, 9F, 9G, 14, 32, 33
Gingko Biloba	1, 7A, 8A, 9D, 14, 17
Green Tea polyphenols	1, 3, 7A, 7D, 7E, 7G, 7H, 9A, 9D, 9E, 32
Vitamin C	1, 4, 6, 7D, 7E, 7F, 9C, 9D, 10A, 14, 18, 32, 33
Vitamin E	1, 4, 5, 7D, 9A, 9B, 19, 21,
Vitamin A	1, 4, 7A 7C, 7D, 14
Indole-3-carbinol	1
Antioxidant carotenoids:	
lutein	1, 4
zeaxanthin	"
lycopene	1, 4, 7D, 7E
beta carotene	"
Antioxidant bioflavonoids:	
quercitin	1
rutin	
naringin	
luteolin	
Eugenol (Tulasi Leaf Extract)	1, 33
L-Taurine (or homotaurine)	1, 7A, 7C, 9A, 15, 25
L-carnitine (or acetyl-L-carnitine)	1, 4, 6, 7D, 7E, 7I, 7L, 9A, 10B, 25
Thioctic acid (α-lipoic acid)	1, 5
N-acetyl-L-cysteine	1, 7F
Cysteine	1, 24, 32
Glutathione	1, 10A

TABLE 2-continued

Formula Components	Functions Functions Listed in Table 3
CoQ10	1, 7A, 22
Creatine phosphate	1, 19
Chondroitin Sulfate	2, 11, 14
Glucosamine Sulfate	2, 6, 11, 14
Cartilage	2, 11, 14, 30
Soy Isolate	2, 4
Protamine Sulphate	2, 11, 14
Vitamin B5 (pantothentic)	4, 14
Vitamin B1	4, 14
Folic Acid	4, 7B
Vitamin B2	4, 14
Vitamin B6	4, 5, 7B
Vitamin B12	4, 7B
Nicotinamide (Vitamin B3)	5
B complex†	4, 7B, 14
Zinc	1, 3, 4, 5, 15, 29, 31, 32
Magnesium	3, 4, 5, 7A, 7L, 15, 16, 31
Calcium	4, 9D, 31
Chromium	1, 4
Selenium	1, 4
Potassium	1, 4, 9D
Strontium	4, 31, 32
Cadmium	4, 32
Manganese	4, 14, 31, 32
Silicon	4, 31, 32
Mineral Complex	4, etc.
Aloe vera	33
Omega-3-fatty acids	1, 6, 7J, 8A, 8B
Essential fatty acids	1, 7D
Vitamin K1	1, 7C, 28, 30, 31, 32
Vitamin D3	3, 5, 15, 20
Polysulfated saccharide	14, 32
Melatonin	1, 23
Allicin	7A, 7I, 7J,
Phytosterols	7G
Fenugreek Seed (D)	3, 7D, 7E, 7I
Gymnema Sylvestre (D)	2, 3
L-lysine	4, 28, 31
L-arginine	1, 4, 14, 25, 26, 27
Glycine	6D, 6E, 23, 25, 26
L-alanine	4, 24
L-methionine	4, 6D, 6E, 24, 25
L-tryptophan	4, 23, 24
L-proline	4, 26
L-tyrosine	4, 25
Gamma-aminobutryic acid	23, 25
Branched Chain Amino Acids*	1, 4, 14, 26, 30
Betain HCl	12, 13
Pepsin	12, 13
Sodium Bicarbonate	13, 32

†B complex = Vit. B1, Vit. B2, Vit. B3, Vit. B5, Vit. B6, and Vit. B12.
*Branched Chain Amino Acids = L-leucine, L-isoleucine, and L-valine.

[0505]

TABLE 3

Preferred Dosage Ranges for Exemplary Formula Components of this Invention

Formula Components	Average Adult Daily Dose (dose/day)
Pine Bark Extract (<85% OPC)	3–2,000 mg
Bilberry Extract (25% OPC)	5–1,500 mg
Grape Seed Extract (95–100% OPC)	5–2,000 mg
Gingko Biloba (24%)	5–1,500 mg
Green tea polyphenol	10–10,000 mg

TABLE 3-continued

Preferred Dosage Ranges for Exemplary Formula Components of this Invention

Formula Components	Average Adult Daily Dose (dose/day)
Vitamin C (ascorbic acid)	10–5,000 mg
Vitamin E (D-alpha-tocopheryl acetate)	5–800 mg
Vitamin A	1,000 IU–25,000 IU
Antioxidant carotenoids:	
lutein	1–300 mg
zeaxanthin	1–300 mg
lycopene	1–300 mg
beta carotene	10–100,000 IU
Quercitin (and other antioxidant bioflavanoids)	1–2,000 mg
Eugenol (Tulasi leaf extract)	1–3,000 mg
Taurine (homotaurine)	5–7,000 mg
Thioctic acid (α-lipoic acid)	5–1,000 mg
N-acetyl-L-cysteine	5–3,000 mg
L-cysteine	1–2,000 mg
Glutathione	1–1,000 mg
CoQ10	4–400 mg
Chondroitin Sulfate	10–10,000 mg
Glucosamine Sulfate	10–10,000 mg
Soy Isolate	50–1,500 mg
Protamine Sulphate	10–900 mg
Vitamin B5 (pantothentic)	1–200 mg
Vitamin B1	10 μg–100 mg
Folic Acid	100 μg–1,500 mg
Vitamin B2 (Riboflavin)	1 μg–50 mg
Vitamin B6 (Pyridoxine HCl)	1 μg–200 mg
Vitamin B12 (Cyanocobalamin 1%)	1 μg–100 mg
Nicotinamide (Vitamin B3, nicotinamide ascorbate)	1–500 mg
B complex†	1–500 mg
Calcium (Krebs)	10–10,000 mg
Zinc (Krebs)	10–3,000 mg
Magnesium (Krebs)	3–10,000 mg
Chromium picolinate	2 μg–50 mg
Selenium (1-selenomethionine)	1 μg–50 mg
Potassium citrate	30–18,000 mg
Strontium	1 μg–800 mg
Cadmium	1 μg–500 mg
Manganese (Krebs)	10 μg–100 mg
Silicon (magnesium trisillicate)	10 μg–200 mg
Mineral Complex	1–50,000 mg
Aloe vera (powder)	10–50,000 mg
Omega-3-fatty acids (flax seed powder)	10–30,000 mg
Essential fatty acids (linoleic acid)	10–10,000 mg
Vitamin D3	1–10,000 IU
Polysulfated saccharide	7–10,000 mg
Melatonin	1–100 mg
L-carnitine (Acetyl-L-carnitine)	10–3,000 mg
Indole-3-carbinol	1–1,000 mg
Phytosterols (Cholestatin III)	10–3,000 mg
Creatine phosphate	10–20,000 mg
Fenugreek Seed (powder)	10–30,000 mg
Gymnema Sylvestre	10–3,000 mg
Vitamin K1	15 μg–75 μg
L-lysine	10–13,000 mg
L-arginine	10–9,000 mg
L-alanine	10–12,000 mg
Glycine	10–9,000 mg
L-methionine	10–300 mg
L-tryptophan	10–3,000 mg
L-proline	10–6,000 mg
L-tyrosine	10–6,000 mg
Gamma-aminobutryic acid	10–12,000 mg
Branched Chain Amino Acids*	10–70,000 mg
Betain HCl	1–10,000 mg
Pepsin	1–10,000 mg
Sodium Bicarbonate	1–10,000 mg

TABLE 3-continued

Preferred Dosage Ranges for Exemplary Formula Components of this Invention

Formula Components	Average Adult Daily Dose (dose/day)

†B complex = Vit. B1, Vit. B2, Vit. B3, Vit. B5, Vit. B6, and Vit. B12.
*Branched Chain Amino Acids = L-leucine, L-isoleucine, and L-valine.

[0506]

TABLE 4

Exemplary Diabetic Compliations Formulation Dosages

COMPONENT	AVERAGE ADULT DOSE PER DAY - mg/day FORMULATION A	AVERAGE ADULT DOSE PER DAY - mg/day FORMULATION B
Bilberry Extract, 25% OPC	375	375
Calcium (Krebs)	500 (110 active)	500 (110 active)
Chondroitin Sulfate	750	750
Chromium Picolinate	200 μg (24.60 μg active)	200 μg (24.60 μg active)
CoQ10	20	20
Fenugreek Seed Powder	150	150
Flax Seed Powder	500	500
Folic Acid	800 μg	450 μg
Linoleic Acid	25	25
Ginko Biloba 24%	25	25
Gymnema Sylvestre	250	250
Taurine or Homotaurine	100	100
Grape Seed extract, 95–100% OPC	100	100
Acetyl-l-carnitine	50	50
Lutein	120	120
Magnesium (Krebs)	300 (48 active)	300 (48 active)
N-Acetyl-l-cysteine	200	200
Pine Bark Extract (greater than 85% OPC)	20	20
Phytosterol Complex (Cholestatin III)	200	200
Potassium Citrate	90 (32.4)	90 (32.4)
Protamine Sulfate	50	50
Shark Cartilage 100%	1,000	1,000
Soy Isolate	1,000 (920 active)	1,000 (920 active)
Green Tea Polyphenols	100	100
Lipoic Acid	20	20
Vitamin A (Acetate Formula A) (Palmitate Formula B)	5,000 iu	5,000 iu
Vitamin B-2 (Riboflavin)	3	50
Vitamin B-6 (Pyridoxine hydrochloride)	4.88 active (4.0 active)	213.4 (175 active)
Vitamin B-12 (Cyanocobalamin 1%)	100 μg active	100 μg active
Vitamin C (Ascorbic acid)	1,000	1,000
Vitamin E, d-alpha tocopheryl acetate	714 (500 iu active)	714 (500 iu active)
Zinc (Krebs)	30 (9 active)	30 (9 active)

I claim:

1. A composition for amelioration of the symptoms and conditions associated with microangiopathy or macroangiopathy which comprises:

(a) a plant extract having antioxidant effect comprising bioflavonoids in an amount effective for providing said antioxidant effect; and

(b) a neovascular regulator that is an inhibitor of angiogenesis.

2. The composition of claim 1 wherein said neovascular regulator is chondroitin sulfate.

3. The composition of claim 1 which comprises antioxidant bioflavonoid plant extracts from at least two different plant sources.

4. The composition of claim 3 wherein said neovascular regulator is chondroitin sulfate and said composition further comprises a glucosamine.

5. The composition of claim 4 which comprises Pine bark extract in an amount effective for providing an antioxidant effect.

6. The composition of claim 1 for prevention and treatment of diabetic complications of microangiopathy which comprises:

(a) antioxidant components:

Pine bark extract;

Bilberry extract;

Tea polyphenols;

Vitamin C; and

Vitamin E.

in a combined amount effective for providing an antioxidant effect;

(b) Neovascular regulator components chondroitin sulphate and glucosamine sulphate in a combined amount effective for inhibiting angiogenesis and/or stabilization of the collagen matrix; and

(c) absorbable zinc and absorbable chromium in an amount effective for compensation of nutrient deficiency.

7. The composition of claim 1 for prevention and treatment of diabetic complications of microangiopathy which comprises:

(a) antioxidant components:

a plant extract having antioxidant effect;

an antioxidant carotinoid;

an antioxidant flavonoid;

thiotic acid;

Vitamin C;

Vitamin E; and

Vitamin A

in a combined amount effective for providing an antioxidant effect and/or for stimulating collagen synthesis;

(b) neovascular regulators and/or factors for collagen synthesis:

chondroitin sulphate, and

glucosamine sulphate

in a combined amount effective for neovascular regulation and/or stimulating collagen synthesis;

(c) minerals:

absorbable zinc;

absorbable chromium;

absorbable magnesium; and

absorbable calcium

in an amount effective for compensating for nutritional deficiency.

8. The composition of claim 7 further comprising:

Gymnema sylvestre;

Fenugreek seed; and

Ginkgo biloba

each present in an amount effective for providing therapeutic and/or protective function.

9. The composition of claim 8 which comprises the components for formula IJ, each present in an amount effective for providing therapeutic and/or protective function.

10. The composition of claim 1 for wound healing which comprises:

(a) a plant extract having antioxidant effect in an amount effective for providing an antioxidant effect;

(b)) chondroitin sulphate and glucosamine sulphate in a combined amount effective for providing for neovascular regulation and/or for promotion of collagen synthesis;

(c) absorbable magnesium in an amount effective for promotion of collagen synthesis.

11. The composition of claim 10 which comprises:

Pine bark extract;

Grape seed extract;

Tea polyphenols;

chondroitin sulfate;

glucosamine sulfate;

Vitamin C;

absorbable magnesium

each component present in an amount effective for providing therapeutic or protective effect.

12. The composition of claim 11 further comprising aloe vera in an amount effective for producing a beoefit for wound healing.

13. The composition of claim 12 further comprising:

Gymnema sylvestre;

Fenugreek seek;

thiotic acid; and

absorbable chromium

each in an amount effective for providing a therapeutic and/or protective effect.

14. A wound healing ointment comprising a composition of claim 10 having the components:

a plant extract having antioxidant effect;

chondroitin sulphate;

Glucosamine sulphate; and

thiotic acid;

each in an amount effective for providing a therapeutic and/or protective effect in a carrier suitable for topical application.

15. The composition of claim 10 which comprises the components of Formula IIG each present in an amount effective for providing a therapeutic and/or protective effect.

16. The composition of claim 1 for treatment and/or prevention of neuropathy which comprises:

(a) a plant extract having antioxidant effect comprising bioflavonoids in an amount effective for providing an antioxidant effect;

(b) a neovascular regulator; and

(c) a source of glucosamine present in a combined amount effective for providing a therapeutic or protective effect.

17. The composition of claim 16 which comprises:

Pine bark extract;

chondroitin sulphate;

glucosamine sulphate;

absorbable magnesium;

absorbable calcium;

thiotic acid;

Ginkgo biloba;

tea polyphenols;

Vitamin C; and

a source of essential fatty acids;

each component present in an amount effective for providing a therapeutic and/or protective effect.

18. The composition of claim 17 further comprising:

Gymnema sylvestre;

Fenugreek seed; and

absorbable chromium.

19. The composition of claim 18 formulated for topical application.

20. A composition according to claim 1 for prevention and/or treatment of cardiovascular disease which comprises:

(a) a plant extract having antioxidant effect comprising bioflavonoids in an amount effective for providing an antioxidant effect;

(b) a neovascular regulator for providing for inhibition of angiogenesis and/or stimulation of collagen synthesis in an amount effective for providing a therapeutic and/or protective effect; and

(c) absorbable zinc present in an amount effective for compensating for nutrient deficiency.

21. The composition of claim 20 which comprises:

Vitamin C;

Vitamin E;

Bilberry Extract;

Pine bark extract;

Tea polyphenols;

soy isolate;

chondroitin sulphate;

Glucosamine sulphate; and

absorbable zinc

each component present in an amount effective for providing a therapeutic and/or protective effect.

22. The composition of claim 21 further comprising:

Gymnema sylvestre;

Fenugreek seed; and

absorbable chromium.

23. A composition for treatment and/or prevention of dental caries and periodontal disease which comprises:

(a) a plant extract having antioxidant effect in an amount effective for providing an antioxidant effect;

(b) absorbable calcium in an amount effective for compensation of nutrient deficiency; and

(c) a Vitamin D3 derivative or analog that induces substantially no hypercalcification in an amount effective for providing a therapeutic and/or protective effect.

24. The composition of claim 23 which comprises:

Pine bark extract;

Tea polyphenols;

absorbable calcium; and

22-oxy-Vitamin D3

each component present in an amount effective for providing a therapeutic and/or protective effect.

25. The composition of claim 24 further comprising:

Gymnema sylvestre;

Fenugreek seed; and

absorbable chromium.

26. The composition of claim 1 further comprising:

ginger;

allicin;

licorice extract;

each present in an amount effective for providing a therapeutic and/or protective effect.

27. A method for treating and/or preventing a symptom condition or disorder associated at least in part with microangiopathy and/or macroangiopathy in an individual having microangiopathy or macroangiopathy which comprises the step of administering to said individual the composition of claim 1.

28. A method for treating and/or preventing symptoms, conditions or disorders associated with diabetic microangi

opathy in an individual having diabetic microangiopathy which comprises the step of administering to said individual the composition of claim 6.

29. A method for treatment of slow to heal or recurrent wounds in an individual having such wound which comprises the step of administering to said individual the composition of claim 10.

30. A method for treatment and/or prevention of cardiovascular disease in an individual having such disease or at risk of developing said disease which comprises the step of administering to said individual the composition of claim 20.

31. A method for treatment and/or prevention of neuropathy in an individual having said condition or at risk of developing said condition which comprises administering to said individual the composition of claim 16.

32. A method for treatment and/or prevention of dental caries, periodontal disease and other gum disorders in an individual having such disease or condition which comprises the step of administering to said individual the composition of claim 23.

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